This supplement was sponsored by Primary Care Education Consortium. The CME articles were sponsored by the Illinois Academy of Family Physicians/Family Practice Education Network and Primary Care Education Consortium.

It was edited and peer reviewed by *The Journal of Family Practice.*

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SUPPLEMENT TO
THE JOURNAL OF
FAMILY PRACTICE®

VOL 64, NO 12 | DECEMBER 2015 | www.jfponline.com

A SPECIAL SUPPLEMENT ON

Hot Topics in Primary Care

Hot Topics in Primary Care

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Management of Opioid-induced Constipation is sponsored by PCEC and supported by funding from AstraZeneca.

Colorectal Cancer Screening is sponsored by PCEC and supported by funding from Exact Sciences Corporation.

Individualizing Pharmacologic Management of Irritable Bowel Syndrome is sponsored by PCEC and supported by funding from Forest Laboratories, Inc., and Ironwood Pharmaceuticals.

Familial Hypercholesterolemia in Youth is sponsored by PCEC and supported by funding from AstraZeneca.

Update on the Recognition and Management of Gout: More Than the Great Toe is sponsored by PCEC and supported by funding from AstraZeneca.

Pharmacologic Approach to Obesity Management is jointly sponsored by the Illinois Academy of Family Physicians/Family Practice Education Network and PCEC and supported by educational grants from Novo Nordisk, Inc. and Takeda Pharmaceuticals U.S.A., Inc.

Ambulatory Glucose Monitoring is sponsored and developed by PCEC.

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Role of the Kidney and SGLT-2 Inhibition in Type 2 Diabetes Mellitus is sponsored by PCEC and supported by funding from Janssen Pharmaceuticals, Inc.

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Nonsteroidal Anti-inflammatory Drugs and Cardiovascular Risk: Where Are We Today? is sponsored and developed by PCEC.

Individualizing Inhaled Medications for Asthma and Allergic Rhinitis is sponsored by PCEC and supported by funding from Teva Pharmaceuticals USA, Inc.

We would like to acknowledge Abbott Diabetes Care and Bayer for their support in connection with the distribution of this supplement.

EDITORIAL ASSISTANCE AND FACULTY HONORARIUM DISCLOSURE

Editorial support was provided by Gregory Scott, PharmD, RPh. The authors were responsible for all content and editorial decisions and received no honoraria related to the development/presentation of these articles.

Hot Topics in Primary Care

Introduction

Stephen A. Brunton, MD, FAAFP

The diverse array of diseases encountered by family physicians presents significant challenges to provide the best patient care consistent with evolving treatment. This supplement addresses some of these challenges by offering the insights of primary care and sub-specialist physicians about diseases whose management is rapidly evolving or where significant practice gaps exist.

The use of lipid-lowering therapy, particularly statins, has been the subject of ongoing discussion, but less attention has been paid to the critically important issue of appropriate screening. Recently, some organizations within the United States have broken ranks with much of the rest of the world by adopting recommendations for universal lipid screening in children. Guidelines for screening for colorectal cancer are established, but screening remains underutilized. Expanded health care coverage and new screening tests address common patient barriers.

The saga regarding the safety of nonsteroidal anti-inflammatory drugs, particularly related to cardiovascular risk, continues with the US Food and Drug Administration recently taking steps to promote their safe use by health care providers and the public. The management of patients with gout is growing more complex due to an aging population with comorbid disease. In advance of new therapies, individualized use of available medications can ease symptoms and alter disease progression.

Recent guidelines simplify the diagnosis of irritable bowel syndrome and new medications provide further opportunity to individualize patient management. Constipation is a common complication of opioid therapy, but management with conventional therapies is often ineffective. New medications for opioid-induced constipation should help. For patients with obesity, new medications complement lifestyle management and help patients achieve and maintain long-term weight loss. Individualizing inhaled therapy in patients with asthma or allergic rhinitis, young or old, can be daunting. But differences among medications—and delivery devices—make it possible.

The management of patients with diabetes mellitus remains a daily challenge, but treatment advances can help. By targeting the kidney, the sodium glucose cotransporter-2 inhibitors afford a unique pharmacologic approach to the management of type 2 diabetes, but there are important aspects to their selection and use. The evolution of insulin continues with new insulins that help address unmet needs encountered with insulin analogs. The expanding list of medications for type 2 diabetes provides greater opportunity for individualized treatment of older adults, but important differences among medications must be understood to maximize efficacy and improve safety. One avenue for improved treatment of all patients with diabetes mellitus is the use of the ambulatory glucose profile. This profile, which consolidates weeks of blood glucose results, helps the clinician see the forest instead of the trees, thereby enabling better individualization of therapy.

I hope you find *Hot Topics in Primary Care* helpful as you continue to provide the highest quality of care for your patients. ●

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Management of Opioid-induced Constipation

David A. Johnson, MD, MACG, FASGE, FACP; and Charles E. Argoff, MD

SUMMARY

What's known

- Opioid-induced constipation is common and impairs function and quality of life.
- Preventive treatment is generally recommended.
- Although recommended in practice guidelines, the use of fiber, water, and laxatives has limited support from published clinical trials.

What's new

- All causes for constipation, including opioid analgesic use, should be investigated.
- The peripherally acting μ-opioid receptor antagonists methylnaltrexone and naloxegol and the locally acting chloride channel activator lubiprostone have been shown to be effective for many—but not all—patients with acceptable safety, and are FDA-approved for opioid-induced constipation.

INTRODUCTION

Opioid analgesics are commonly used to treat people with a wide variety of pain disorders, including severe acute pain and moderate to severe cancer and noncancer pain.[1] In 2012, 259 million prescriptions were written for opioids in the United States.[2] While opioids can provide effective pain relief for some patients, their use is not without limitations. Constipation is the most common adverse event, affecting an average of 41% of patients taking an oral opioid for up to 8 weeks.[3] Part of a broader constellation of symptoms called opioid-induced bowel dysfunction, opioid-induced constipation (OIC) is "a change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency."[4] OIC can result in hemorrhoid formation, rectal pain and burning, bowel obstruction, bowel rupture, gastroesophageal reflux disease, and death.[5] Moreover, OIC causes significant patient distress, limits work productivity, and diminishes overall health-related quality of life. As a consequence, patients may reduce the dose of or stop taking the opioid.[4,6-8] One study reported that almost half of patients reported moderate to complete interference with pain management resulting from their constipation.[7]

The objectives of this article are to describe the clinical presentation of OIC, means to differentiate OIC from other causes of constipation, and evidence-based options for the treatment of OIC.

OPIOIDS AND THE GASTROINTESTINAL TRACT

The gastrointestinal (GI) effects of opioids arise from direct actions on the GI tract, and to a lesser degree indirect actions through the central nervous system, possibly by altering autonomic outflow.[5] The actions of opioids on the GI tract are mediated primarily via μ receptors; centrally, opioids agonize 4 receptor subtypes: μ, δ, κ, and opioid receptor-like-1.[5]

The enteric nervous system within the gut has a dense concentration of neurons, which supply all layers of the alimentary canal and influence nearly every aspect of the digestive process.[9] Through interactions with enteric μ-opioid receptors, μ-opioid medications cause constipation by inhibiting enteric neuron function.[10] Specific effects include delaying gastric emptying, reducing bowel tone and contractility, and prolonging GI transit time. Opioids enhance fluid absorption by producing more frequent and stronger contractions of the circular muscles, while reducing longitudinal muscle propulsive contractions, leading to harder, drier

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SUPPORT

This article is sponsored by Primary Care Education Consortium and was supported by funding from AstraZeneca.

TABLE Aspects of opioid-induced constipation most (≥80%) patients would prefer to improve[8]

Aspect	Participants in agreement (%)
Be able to have a bowel movement without pain	87.9
Be able to have a soft stool that is not loose or watery	87.1
Not experience rectal straining due to my constipation	83.4
Feel less bloated	83.0
Be more comfortable using my opioid medication without fear of being constipated	82.1
Worry less about being able to have a bowel movement	80.5
Have less pain in my stomach area	80.3

With kind permission from Springer Science+Business Media: *Advances in Therapy*, Patient Preferences for Change in Symptoms Associated with Opioid-Induced Constipation, volume 31, 2014, page 1268, Epstein RS, et al., Table 3.

stools. Difficulty in rectal evacuation stems from the ability of opioids to increase anal sphincter pressure and decrease reflex relaxation in response to rectal distention.[5,9-11] Although these effects of opioids may be useful for treating diarrhea, they often lead to constipation in the absence of diarrhea. OIC also can interfere with digestion and drug absorption.[9]

CLINICAL EVALUATION

Constipation may be due to one or more etiologies. Nonopioid causes of constipation may have existed prior to initiation of opioid therapy, but may not have been reported by the patient. Thus, investigating the cause should extend beyond the existing symptoms and common consequences of OIC to include other etiologies, such as irritable bowel syndrome, slow transit, or an evacuation disorder, or secondary causes, such as medications, neuropathic or myopathic disorders, and endocrinopathies.[12,13]

A complete medical history is essential to investigate nonopioid causes of constipation. In addition to medication (both prescription and nonprescription) use, the patient should be questioned about dietary and lifestyle habits. The history should also establish when symptoms of constipation first emerged and their timing relative to opioid initiation.[12] The Bristol Stool Form Scale is useful to categorize stool based on appearance.[14] Of the 7 types of stools, types 1 and 2 indicate constipation; 3 and 4 are ideal; and 5, 6, and 7 indicate diarrhea.

A physical examination that includes a digital rectal examination to assess relaxation of the anal sphincter and pelvic floor on straining should be performed as part of the assessment of pelvic floor dysfunction. Symptoms of pelvic floor dysfunction include excessive straining, prolonged time to defecate, need for digital evacuation, and persistent symptoms despite loose stools with laxatives. In addition to pelvic floor dysfunction, other situations in which further testing is warranted include unexplained weight loss, rectal bleeding, colorectal cancer, or constipation refractory to conventional treatment. Laboratory testing is useful to exclude metabolic disorders.[13]

MANAGEMENT

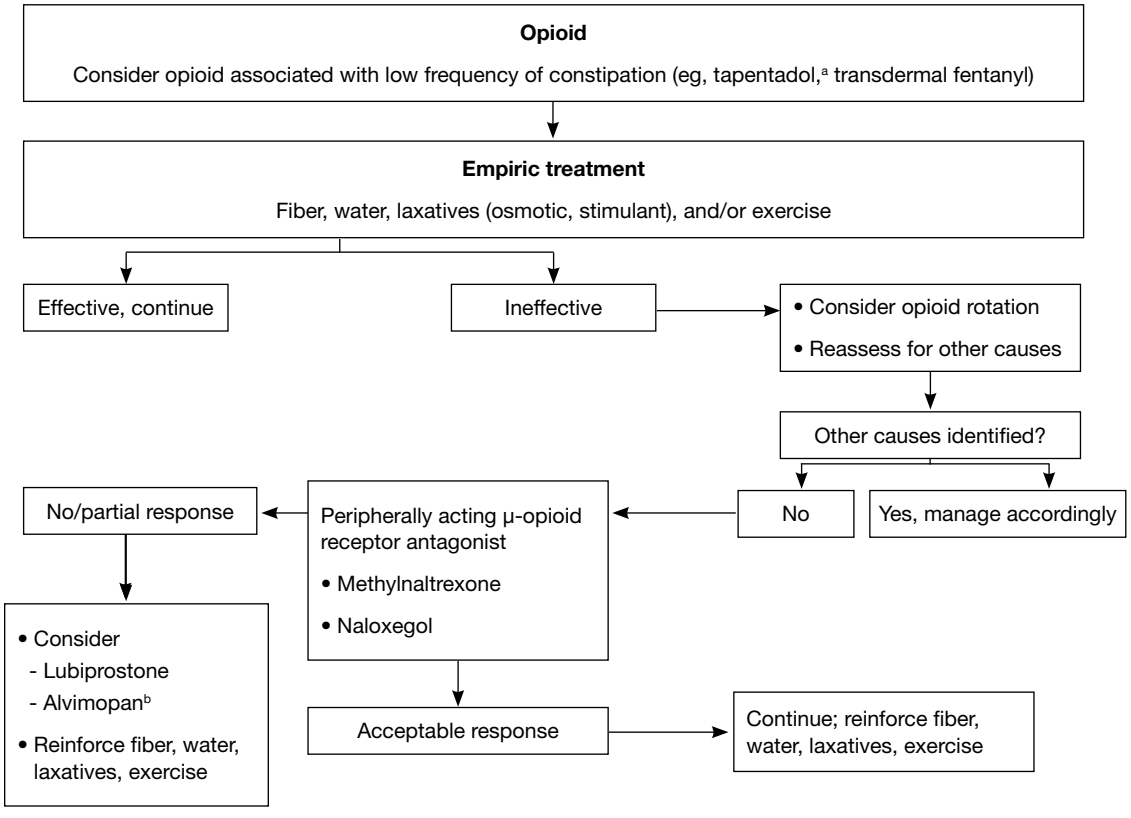
Several factors should be kept in mind when managing patients with OIC. First, tolerance to the constipating effects of opioids generally does not occur; thus, OIC may last as long as opioid therapy is continued.[5,10] For this reason, coupled with the high prevalence of OIC in patients taking an opioid, strong consideration should be given to beginning preventive therapy at the time opioid therapy is initiated, particularly for older adults or others with additional reasons for developing constipation.[1,3,15] Another factor to keep in mind when initiating opioid therapy is that constipation may occur at opioid doses lower than those required for analgesia. Thus, merely lowering the opioid dose may not be effective for managing OIC, while the analgesic benefit of the prescribed opioid may be lessened or lost.[13]

Patient preferences for symptom improvement should also be identified and treatment individualized. A survey of 513 patients with chronic pain who were experiencing OIC demonstrated 7 aspects of constipation that ≥80% of patients would prefer to improve (**TABLE**).[8] Additionally, more than 70% of the patients surveyed indicated that it was very or extremely important that they have one additional bowel movement per week.

Initial management

The goal of initial management is to prevent OIC from the time opioid therapy is begun. A suggested algorithm developed by the authors is shown in the **FIGURE**. One approach is the empiric use of laxatives, fluids, and other options.[5] Another approach is to use an opioid associated with a lower rate of constipation. Among the opioids, transdermal fentanyl and tapentadol, a dual μ-opioid receptor agonist and norepinephrine reuptake inhibitor approved for acute pain, have been shown to cause less impair-

FIGURE Suggested strategy for managing constipation in a patient taking an opioid for chronic noncancer pain



[a]Approved for acute pain in the United States.

[b]Not approved for opioid-induced constipation in the United States; availability subject to a Restricted Access Program.

ment of bowel function. If the patient experiences constipation with one opioid, switching to another opioid may result in less severe constipation. This process of switching to another opioid, also called opioid rotation, is complicated by the need for utilizing equianalgesic doses and must take into account the possibility of tolerance to the current opioid.

Opioid selection

Some medical evidence suggests that specific opioids may be less constipating than others.[13,16] A randomized, open-label, 28-day crossover trial of 212 patients with noncancer pain showed significantly better pain relief with transdermal fentanyl than sustained-release oral morphine, while constipation occurred in fewer patients with fentanyl than with morphine (16% vs 22%).[17] Reduced bowel function, as confirmed by the bowel function questionnaire, was less common among users of transdermal fentanyl (29% fentanyl vs 48% morphine; *P*<.001). Similar results were observed in another randomized, open-label, 30-day crossover study involving 202 patients with cancer treated with transdermal fentanyl and sustained-release oral morphine.[18] Both provided similar pain relief, but significantly fewer patients treated with fentanyl experienced constipation (27.2% vs 44.5%, respectively; *P*<.001).

Several studies have demonstrated tapentadol to be less constipating than roughly equianalgesic doses of oxycodone immediate-release and sustained-release.[19-22] In patients with lower back pain or osteoarthritis, tapentadol consistently caused less impairment of bowel function than oxycodone, with scores for tapentadol similar to those for

placebo over 90 days.[21] Compared with oxycodone, patients treated with tapentadol experienced significantly fewer days without a bowel movement, softer stools, less straining, less laxative use, and fewer abdominal, rectal, stool, and overall symptoms.[21]

Laxatives and lifestyle changes

A broad array of management options are available, yet only limited clinical trial data, particularly for OIC, support the use of conventional agents such as stool softeners, osmotic laxatives, and stimulant laxatives, as well as increased fluid and fiber intake and other lifestyle changes.[1,12,13,15,23] Nonetheless, current guidelines issued by pain specialists recommend initial treatment with bowel regimens that include these options, as they are perceived as often being effective. No specific recommendations are provided in the guidelines regarding the agents and doses to be used.[1,15]

Pharmacological therapy

An increasing number of opioid antagonists and other options are available for the treatment of OIC, generally supported by clinical trial evidence demonstrating their benefits and limitations for OIC.

One of the most widely used opioid antagonists, naloxone has been combined with the opioid agonists buprenorphine, oxycodone, and pentazocine to minimize the risk of abuse. The combination of naloxone and oxycodone has demonstrated beneficial effects on bowel function with no effect on analgesia. It was approved for severe pain in the United States in 2014, but is not yet commercially available.[24-27] Experience with buprenorphine/naloxone and pentazocine/naloxone for OIC is limited. None of the combination therapies are approved for OIC in the United States.

Peripherally acting μ-opioid receptor antagonists

Medications that serve as competitive antagonists of peripheral μ-opioid receptors are an option for adjunctive therapy for OIC. These include methylnaltrexone, naloxegol, and alvimopan.

Methylnaltrexone

Methylnaltrexone was approved in 2008 by the US Food and Drug Administration (FDA) for the management of OIC in palliative care and has recently been approved for the treatment of OIC in adults with chronic noncancer pain. Laxation within 4 hours has been observed in 48% of patients with OIC in advanced illness after subcutaneous administration of a single dose of methylnaltrexone 0.15 mg/kg, compared with 15% for placebo.[28] Over the 2 weeks of treatment, rescue-free laxation within 24 hours of each of the 7 doses occurred in 55% to 66% of the methylnaltrexone group and 29% to 39% of the placebo group. Most adverse events involved the GI tract, with those occurring more commonly with methylnaltrexone (methylnaltrexone vs placebo): abdominal pain (17% vs 13%), flatulence (13% vs 7%), nausea (11% vs 7%), and diarrhea (6% vs 4%).

Similar benefits have been observed in patients with OIC and chronic noncancer pain.[29] Patients received methylnaltrexone 12 mg once daily or every other day (alternating with placebo) or placebo for 4 weeks. Within 4 hours of the first dose, 34.2% of patients in both methylnaltrexone groups had a rescue-free bowel movement compared with 9.9% of patients receiving placebo. Both methylnaltrexone groups had significantly shorter time to first rescue-free bowel movement and greater increase in number of weekly rescue-free bowel movements compared with placebo. Bristol Stool Form Scale scores and sensation of complete evacuation were significantly superior with methylnaltrexone once daily. Significantly greater improvement in patient-reported, constipation-specific quality of life was seen in both methylnaltrexone groups. Adverse events included abdominal pain, diarrhea, nausea, and hyperhidrosis.

Naloxegol

Naloxegol is a pegylated derivative of naloxone with increased oral bioavailability and peripheral selectivity, with negligible penetration of the blood–brain barrier.[30] Naloxegol was approved in 2014 by the US FDA for the treatment of OIC in adults with chronic noncancer pain. In 2 identically designed double-blind, parallel-group, phase 3 studies, outpatients with OIC who had been taking an oral opioid for noncancer pain at a stable daily dose of 30 to 1000 mg of morphine-equivalents for 4 weeks or longer were randomized to naloxegol 12.5 or 25 mg or placebo once daily for 12 weeks.[30] The primary endpoint was the 12-week response rate, ie, ≥3 spontaneous bowel movements per week and an increase from baseline of ≥1 spontaneous bowel movements for ≥9 of 12 weeks and for ≥3 of the final 4 weeks.

A significantly higher response rate compared with placebo was observed with naloxegol 25 mg in both studies and with naloxegol 12.5 mg in one study.[30] Other benefits observed with naloxegol compared with placebo included a reduction in the time to the first spontaneous bowel movement, increase in the mean number of days per week with one or more spontaneous bowel movements, and increase in the mean number of spontaneous bowel movements per week. Greater improvements in straining, stool consistency, and frequency of days with complete spontaneous bowel movements also were observed at the 25-mg dose in both studies and at the 12.5-mg dose in one of the 2 studies.

In both studies combined, an adverse event was observed in 54.6% and 65.2% of the patients receiving naloxegol 12.5 and 25 mg, respectively, and 53.2% of patients receiving placebo. Most adverse events involved the GI tract. A serious adverse event occurred in 5.7%, 3.4%, and 5.2% of patients in the naloxegol 12.5 mg, naloxegol 25 mg, and placebo groups, respectively, and was similar in type and frequency across the 3 groups.[30]

The long-term safety and tolerability of naloxegol 25 mg once daily were compared with investigator-chosen laxative treatment (usual care) in an open-label, 52-week study of 804 patients with noncancer pain and OIC.[31] Patients were taking an opioid at a dose of 30 to 1000 morphine-equivalents per day for ≥4 weeks. An adverse event occurred in 81.8% of patients treated with naloxegol 25 mg and 72.2% of patients treated with usual care over the 52 weeks of the study. Treatment-emergent adverse events primarily involved the gastrointestinal tract and consisted of (naloxegol vs usual care) abdominal pain (17.8% vs 3.3%), diarrhea (12.9% vs 5.9%), nausea (9.4% vs 4.1%), back pain (9.0% vs 8.9%), headache (9.0% vs 4.8%), flatulence (6.9% vs 1.1%), arthralgia (6.2% vs 5.9%), nasopharyngitis (6.2% vs 5.6%), upper respiratory tract infection (5.8% vs 8.5%), bronchitis (5.6% vs 4.4%), vomiting (5.1% vs 5.6%), upper abdominal pain (5.1% vs 1.1%), sinusitis (4.3% vs 7.0%), and urinary tract infection (4.1% vs 8.1%).

A serious adverse event occurred in 9.6% of patients receiving naloxegol and 11.1% of patients receiving usual care. Two patients in each group experienced a major adverse cardiovascular event judged to be unrelated to study treatment. Two patients treated with naloxegol experienced symptoms of opioid withdrawal, both of which were attributed to a change in opioid dose.

Alvimopan

Alvimopan is another peripherally acting μ-opioid receptor antagonist. Although it is not approved for OIC, the efficacy and safety of alvimopan in patients with opioid-induced bowel dysfunction have been demonstrated in patients with noncancer pain in clinical trials lasting up to 6 weeks.[32,33] Alvimopan is for use in hospitals for up to 7 days to accelerate GI recovery after surgeries that include partial bowel resection with primary anastomosis. Long-term use of alvimopan is associated with an increased incidence of myocardial infarction. Accordingly, alvimopan is available only through a restricted program for short-term use.[34]

Chloride Channel Activator

Lubiprostone

Approved by the US FDA in 2013 for OIC, lubiprostone is a locally acting chloride channel activator that bypasses the antisecretory action of opioids and enhances chloride-rich intestinal fluid secretion.[35] As a consequence, lubiprostone softens stools and facilitates the passage of stool. This effect may be reduced in methadone-treated patients.[36]

In a phase 3 double-blind study, patients treated with stable doses of an opioid for chronic noncancer pain were randomized to lubiprostone 24 mcg twice daily or placebo for 12 weeks.[35] The overall change from baseline to week 8 in the mean number of spontaneous bowel movements was significantly greater with lubiprostone than placebo (2.2 vs 1.6, respectively; *P*=.004). At week 12, the difference between the 2 groups was not significant due to the high dropout rates (lubiprostone [32.9%] and placebo [30.3%]). Significantly more patients treated with lubiprostone achieved a spontaneous bowel movement within 24 (*P*=.018*)* and 48 (*P*=.05) hours of the first dose. Compared with placebo, patients treated with lubiprostone showed significantly greater improvement in abdominal discomfort, straining, constipation severity, and stool consistency. An adverse event was experienced by 63.5% of patients receiving lubiprostone and 54.4% of patients receiving placebo. Nausea, diarrhea, and abdominal distention were the most frequently reported adverse events and were common reasons for treatment discontinuation.

Lubiprostone 24 mcg twice daily has also been compared with sennosides once daily in patients (N=60) with self-reported constipation taking an opioid for pain control after orthopedic surgery.[37] After 7 days of treatment, the mean changes in bowel symptoms did not differ between the 2 groups, except for completeness of bowel movement and reduction of abdominal pain, both favoring sennosides. An adverse event was experienced by 45.2% of patients treated with lubiprostone and 41% of patients treated with sennosides. Gastrointestinal adverse events that were the most common (in the lubiprostone and sennosides groups, respectively) included the following: nausea (9.7% vs 17.2%), diarrhea (16.1% vs 6.9%), abdominal pain (25.8% vs 6.9%), abdominal cramping (19.4% vs 20.7%), and constipation (0% vs 3.4%).

SUMMARY

Constipation is a common complication of opioid therapy that contributes to substantial patient morbidity, decreased productivity, and opioid nonadherence. Other causes of constipation may occur concomitantly and should be investigated. Although evidence supporting their use is limited, the use of fiber, water, laxatives, and/or exercise is recommended in current guidelines as initial management. Peripherally acting μ-opioid receptor antagonists are important treatment options, are well-tolerated, and improve many signs and symptoms of OIC in patients taking an opioid for chronic noncancer pain. ●

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Colorectal Cancer Screening

Adam B. Elfant, MD, FACG

CASE STUDY: JS is a 54-year-old male with an average risk of colorectal cancer (CRC). In discussion with his primary care physician, JS is found to have limited knowledge about CRC and its consequences. He has heard "horror stories" about the bowel preparatory regimen for colonoscopy and wants no part of it. He also does not like the idea of a tube being inserted into his rectum due to concern of perforation. He generally follows his doctor's advice and adheres to prescribed therapy. His blood pressure is well-controlled with a diuretic and angiotensin receptor blocker.

EPIDEMIOLOGY

In the United States, CRC is the third leading cause of death from cancer in males and females, and the second leading cause of cancer deaths overall.[1] Non-Hispanic blacks have the highest mortality rate from CRC (males, 28.4; females, 18.9 per 100,000 population), which is approximately 50% higher than non-Hispanic whites.[1] The lifetime probability of developing invasive CRC is approximately 1 in 20 people.[1] At diagnosis, 40% of CRCs are classified as localized, involving the mucosa and limited to the bowel wall, 36% as regional involving local lymph nodes, and 20% are associated with distant metastases, primarily to the liver. This significant number of patients with advanced stage disease suggests that diagnosis is often delayed.[1]

It is generally felt that it may take up to 10 to 15 years for the progression of adenomatous cells to CRC.[2] Delay in diagnosis is particularly unfortunate since:

- Early diagnosis correlates with better survival: the 5-year survival rates for CRC are 90% for localized, 71% for regional, and 13% for metastatic.[1]
- Removal of colonic adenomas has been shown to reduce the incidence of CRC by more than 75% over an average of 5.9 years of follow-up and 53% after a median of 15.8 years of follow-up.[3,4]
- There is direct evidence from randomized controlled trials that endoscopic evaluation and fecal occult blood tests reduce mortality from CRC.[5]

It is clear that identifying individuals with adenomatous polypoid disease prior to malignant progression to CRC is critically important to prevent morbidity and mortality. For this to occur, patients must undergo screening. However, the national CRC screening rate in 2013 was 58% for adults ages 50 to 75 years, suggesting that significant barriers to screening exist. [6] Among these barriers, unspecified fears, concerns about the bowel preparation, lack of knowledge, and pain are the most important.[7] Barriers to screening are not homogeneous across all tests, however.[8] Bowel preparation was the primary barrier to colonoscopy and flexible sigmoidoscopy, while lack of health care provider recommendation was the primary barrier to the fecal occult blood test.

This article discusses the current recommendations for CRC screening and the available testing options.

CURRENT SCREENING RECOMMENDATIONS

Risk factors

Adults should be individually assessed for their risks of CRC as risk determines when to begin screening. A detailed history is a key step in assessing risk for CRC. Identified risk factors include increasing age, type 2 diabetes mellitus, lifestyle factors such as a diet high in red meat, physical inactivity, obesity, smoking, and heavy alcohol use, as well as some racial and ethnic groupings (African American race, Ashkenazi Jewish ethnicity). People with any of the following conditions are at increased risk of developing CRC: a personal history of colorectal polyps, CRC, or inflammatory bowel disease, as are individuals with a family history of CRC, adenomatous polyps, or various inherited syndromes such as familial adenomatous polyposis (FAP) or hereditary non-polyposis colon cancer (HNPCC).[2,9] A high-risk family history is considered as one first-degree relative developing CRC before the age of 60 years or 2 or more first-degree relatives developing CRC at any age.

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DISCLOSURES

Dr. Elfant discloses that he is on the advisory board and speakers' bureau for Exact Sciences Corporation.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from Exact Sciences Corporation.

TABLE 1 Current recommendations for colorectal cancer screening in average-risk individuals

	Who		Recommended tests & frequency[a]						
			Invasive				Noninvasive		
	Beginning age	Until age	C	FS	CTC	DCBE	High sensitivity gFOBT	FIT	Multi-target sDNA
USPSTF 2008[10,b]	50 y	75 y	10 y	5 y			1 y	1 y	
American College of Physicians 2012[9]	50 y	75 y or life expectancy <10 y	10 y	5 y			1 y	1 y	UC[c]
American Cancer Society 2015[2]	50 y	NS	10 y	5 y	5 y	5 y	1 y	1 y	3 y

[a]Assumes no evidence of disease.

[b]Currently being updated.

[c]Guideline cited that limited data prevent determining an appropriate interval between screening.

Abbreviations: C, colonoscopy; CTC, computed tomographic colonography; DCBE, double-contrast barium enema; FIT, fecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac-based fecal occult blood test; NS, not specified; sDNA, stool DNA test; UC, uncertain; USPSTF, United States Preventive Services Task Force.

Age at initial screening

US guidelines recommend initial screening for CRC in average-age-risk people at the age of 50 years (**TABLE 1**).[2,5,9,10] In individuals with a family history of CRC in any first-degree relative before age 60 years, screening should start at age 40, or 10 years younger than the age at which the youngest affected relative was diagnosed with CRC, whichever is earlier.[2,5,9] Screening should start even earlier in other high-risk patients such as those with FAP or HNPCC (Lynch Syndrome).[2,5]

Screening tests

Two general categories of screening tests are available, invasive and non-invasive. Invasive tests such as colonoscopy and flexible sigmoidoscopy identify and allow removal of adenomatous polyps and detect cancer directly. Computed tomographic colonography (CTC) is a radiologic test that detects cancer indirectly, but does not allow removal of polyps or biopsy of abnormal lesions. Another radiologic test, double-contrast barium enema, is infrequently used today. A minimally invasive blood plasma DNA test is also available, but has low sensitivity and specificity and is currently not recommended in any guidelines.

US Food and Drug Administration (FDA)-approved noninvasive tests are currently stool-based and potentially detect cancer through detection of fecal blood alone or alterations in exfoliated DNA in combination with hemoglobin. These include 2 fecal occult blood only tests, which can be guaiac-based (gFOBT) (only the high-sensitivity gFOBT is acceptable for screening) or immunochemical-based (FIT). A third type of noninvasive stool test is a multi-target stool DNA (sDNA) test, which uses a combination of altered DNA plus hemoglobin markers to identify underlying neoplasia. The sDNA test has a reported 42% detection rate for advanced adenoma while the FOBT/FIT tests do not have a reported detection rate for these lesions. Colonoscopy is the most reliable test for detection of adenomas.

In addition to the patient's CRC risk status (average vs high-risk), other factors to be considered when selecting a screening test for CRC include patient preference, likelihood of compliance, access to testing, out-of-pocket costs, and sensitivity and specificity of the test (**TABLE 2**). Patient barriers to screening are reduced when a choice of noninvasive tests or colonoscopy is presented and providing choice has been shown to nearly double the annual screening rate compared to colonoscopy alone.[11] Coverage of CRC screening is a required preventive health benefit under the Affordable Care Act of 2009 for health plans that started on or after September 23, 2010. Health insurance plans that began prior to this date may also be required to provide coverage as determined by state laws. However, some costs such as a bowel preparation kit, pathology, or anesthesia, may not be covered under individual plans.[2] Medicare pays for all recommended CRC screening tests included in the United States Preventive Services Task Force guideline and the FDA-approved multi-target sDNA test, but does not cover CTC. Age and other requirements generally apply (**TABLE 3**).[12]

Invasive tests

Colonoscopy

Colonoscopy is generally agreed to be the reference standard for CRC screening as it allows visual examination of the entire large bowel. It is also used as a diagnostic test to evaluate positive screening tests from any other CRC screening strategy. It is also possible to remove polyps in the same session,

TABLE 2 **Performance of screening tests[a]**

		Sensitivity		Specificity
		CRC	Adenomas	
Invasive tests	Colonoscopy[28]	95%	95%	90%
	Flexible sigmoidoscopy[28]	~50% (95% distal only)	~50% (95% distal only)	92%
	Computer tomographic colonography[29-31]	96%	94%	86% to 96%
Noninvasive tests	Fecal immunochemical test[28]	70%	22%	95%
	Fecal occult blood test (Hemoccult SENSA)[28]	70%	24%	93%
	Fecal occult blood test (Hemoccult II)[28]	40%	12%	98%
	Multi-targeted stool DNA test[27]	92%	42%[b]	87%

[a]Results are not from head-to-head trials.

[b]Includes advanced adenomas and sessile serrated polyps measuring ≥1 cm.

Abbreviation: CRC, colorectal cancer.

potentially preventing development of CRC.[5] Colonoscopy is supported by case control and cohort studies, showing that colonoscopy offers the potential to prevent CRC, with its associated morbidity and mortality.[5] Recent evidence indicates that for every 1% increase in colonoscopy screening rate, the risk of death from CRC decreases by 3%.[13]

Colonoscopy also has several factors that must be considered when discussing screening with patients. Foremost is the need for adequate bowel cleansing and the concerns of patients regarding poor palatability and tolerability of bowel cleansing agents and the need to spend significant time before the colonoscopy in the bathroom.[14] The traditional "day before colonoscopy bowel prep" has been replaced with a more effective split-dose preparation taken the evening before and the morning of the colonoscopy and is now the recommended strategy.[5,14] Also necessary is the need for transportation following the procedure due to the use of sedation or anesthesia.[2] Fortunately, the risk of perforation is low with diagnostic colonoscopy, ranging from 0.016% to 0.2%.[15] The risk of perforation increases with age and is greater in people with comorbidities such as diabetes mellitus, chronic pulmonary disease, congestive heart failure, vascular disease, renal insufficiency, liver disease, and dementia.[15]

Flexible sigmoidoscopy

Flexible sigmoidoscopy also enables direct visual examination and polyp removal, but is limited to the rectum and the distal colon due to the limited length of the sigmoidoscope and the ability of the operator to pass the scope to its full length. As with colonoscopy, bowel cleansing is required, although it is less involved for flexible sigmoidoscopy and generally entails enemas the day of the procedure. Sedation is not generally used and intestinal perforation is uncommon.[2]

Recent meta-analyses of randomized controlled trials have concluded that screening by flexible sigmoidoscopy significantly reduces the incidence and mortality of CRC, but only in the distal colon.[16-18] A recent analysis of cancers not detected by flexible sigmoidoscopy showed that of the prevalent but not detected lesions, 37% were beyond the reach of the sigmoidoscope, while 7% were due to inadequate depth of insertion of the sigmoidoscope; 36% were due to problems in patient compliance, and 21% were due to endoscopist limitation.[19]

Computed tomographic colonography

CTC, or virtual colonoscopy, is a promising option for CRC screening. CTC currently requires the same bowel preparation as optical colonoscopy. Although CTC might be considered non-invasive, insertion of a tube into the rectum is required (similar to the tube used for barium enema) to fill the colon with air to enhance lesion detection. Sedation is not required and the risk of complications is low.[2,5] Early experience with CTC showed inferior sensitivity and specificity in direct comparison with colonoscopy.[20] The sensitivity of CTC for detecting lesions at least 6 mm was 39% compared with 99% for colonoscopy, while the specificity of detecting patients without any lesion at least 6 mm was 91% and 100%, respectively. Recent experience comparing laxative-free CTC and colonoscopy has shown comparable sensitivity and specificity for detecting lesions ≥1 cm.[21]

Limitations of CTC are that positive findings require a colonoscopy for evaluation and biopsy; extracolonic findings also require further investigation.[5] The technical aspects of CTC have not yet been standardized and an appropriate screening interval has yet to be determined, although 5 years is the current standard.[5]

TABLE 3 **Overview of screening tests**[2,5,9,12,22]

		Coverage of CRC Screening by Medicare			
	Test	**Frequency**	**Age & Requirements**	**Pros**	**Cons**
Invasive	Colonoscopy	• High risk: every 2 y • Avg risk: every 10 y	• No age restriction • No age restriction but ≥4 y after flexible sigmoidoscopy	• Usually view entire colon • Can biopsy & remove polyps • May diagnose other diseases	• May miss small polyps • Full bowel preparation needed • Pretest dietary and medication restrictions • Expensive procedure • Sedation necessary • May be uncomfortable • May require time off from work • Requires transportation home • Small potential for bleeding, bowel tears, infection
	Flexible sigmoidoscopy	Every 4 y	≥50 y, but >10 y after colonoscopy if average risk	• May not need a full bowel preparation • Sedation usually not necessary • May not require a specialist	• May view only about a third of the colon • May miss small polyps • May not remove all polyps • Pretest dietary and medication restrictions • May be uncomfortable • Small potential for bleeding, bowel tears, infection • Abnormal result requires colonoscopy • May require time off from work
	Computed tomographic colonography	Not covered	Not covered	• May view the entire colon • Sedation not necessary	• May miss small polyps • Full bowel preparation needed • Cannot remove polyps • Some false positive results • Abnormal result requires colonoscopy
	Double-contrast barium enema	• High risk: every 2 y • Avg risk: every 4 y	≥50 y	• May view the entire colon • Sedation not necessary • Reasonably safe	• May miss small polyps • Full bowel preparation needed • Cannot remove polyps • Some false positive results • Abnormal result requires colonoscopy

Noninvasive tests

Guaiac-based fecal occult blood test

The gFOBT has a long history of use for detecting the presence of blood in the stool and is based on the pseudoperoxidase activity of heme in human hemoglobin. A highly sensitive version is now available for CRC screening, but is still subject to false positives since the test detects blood from any source within the digestive tract, including gastric ulcers, upper gastrointestinal bleeding related to aspirin, and hemorrhoidal bleeding, as well as dietary sources. Thus, there are medication and dietary restrictions prior to the test, which may not always be followed by patients. A limitation of gFOBT is that it does not detect lesions that are not bleeding at the time of the test. To minimize false negative findings, it is recommended that the test be conducted on 3 consecutive stool samples, with two specimens collected from different areas of each stool sample.[2,5] A high-sensitivity gFOBT with a sensitivity for cancer >70% and specificity >90% should be used.[22]

TABLE 3 **Overview of screening tests**[2,5,9,12,22] ***(continued)***

		Coverage of CRC Screening by Medicare			
	Test	**Frequency**	**Age & Requirements**	**Pros**	**Cons**
Noninvasive	Guaiac-based fecal occult blood test	Every year	≥50 y	• No direct risk to colon • No bowel preparation • Sampling completed at home	• May miss many polyps and some cancers • Some false positive results • May require pretest dietary and medication restrictions • Abnormal result requires colonoscopy
	Fecal immunochemical test	Every year	≥50 y	• No direct risk to colon • No bowel preparation • No pretest dietary or medication restrictions • Sampling completed at home	• May miss many polyps and some cancers • Some false positive results • Abnormal result requires colonoscopy
	Multi-target stool DNA	Every 3 y	50–85 y typical, asymptomatic average risk for CRC	• Identifies lesions that are not actively bleeding • No direct risk to colon • No bowel preparation • No pretest dietary or medication restrictions • Sampling completed at home	• May miss many polyps and some cancers • Some false positive results • Abnormal result requires colonoscopy

Abbreviation: CRC, colorectal cancer.

Fecal immunochemical test

The FIT or immunochemical fecal occult blood test (iFOBT) is similar to the gFOBT in that it detects blood, except that it directly detects the human globin portion of hemoglobin. As FIT is less likely to detect bleeding from the upper digestive tract due to degradation of the globin moiety, there are no medication or dietary restrictions prior to testing. Use of highly-sensitive versions of the FIT are recommended.[2] Head-to-head comparisons have shown that FIT is more sensitive than high-sensitivity gFOBT.[23-26] Both, however, were less reliable than flexible sigmoidoscopy.[24]

Digital rectal exam by itself is not considered a screen for CRC either with or without a gFOBT or FIT performed on fecal material collected at that time. gFOBT and FIT used for CRC screening should be performed on only passed stool samples to decrease the chance of both false negative and false positive testing.

Multi-target stool DNA test (sDNA)

The multi-target sDNA test detects human DNA alterations (mutations and aberrant methylation) that are known to be associated with bleeding and nonbleeding CRC and pre-cancerous lesions and the non-specific marker, hemoglobin, in stool. DNA is released from cells that are sloughed into the stool. The only multi-target sDNA test currently available (Cologuard) is approved by the FDA for primary CRC screening in individuals ages ≥50 years who are at average risk for CRC. This multi-target sDNA test uses the composite score provided by 11 biomarkers including quantitative molecular assays for 2 DNA methylation markers (*NDRG4* and *BMP3*), 7 DNA mutation markers (all *KRAS*), and 1 DNA normalization marker (*Beta Actin*). A hemoglobin assay is also included to detect blood in the stool. The test composite score provides a single "positive" or "negative" patient result. Individual marker results are not reportable as there are no positive/negative threshold values for individual component markers.

A recent pivotal, prospective, multicenter trial compared the multi-target sDNA test (Cologuard) with FIT (OC FIT-CHEK, Polymedco, Inc.) in people at average risk for CRC who were scheduled to undergo screening colonoscopy, which was used as the reference standard on all subjects.[27] Stool samples were collected prior to routine bowel preparation for the colonoscopy. Results were fully evaluable in 9989 patients and showed that the sensitivity of the sDNA test was

significantly higher than FIT.[27] Specifically, the sDNA test identified 60 of 65 patients identified as having CRC by colonoscopy, while FIT identified 48 of 65 cancers, yielding sensitivities of 92.3% and 73.8%, respectively (*P*=.002). Respective sensitivities were 93.3% vs 73.3% for stage I to III CRC (*P*=.002); 69% vs 46% for the highest risk advanced precancerous lesions, ie, those with high-grade dysplasia (*P*=.004); and 42.4% vs 23.8% for advanced precancerous lesions overall (*P*<.001). Overall specificity was 86.6% for the sDNA test and 94.9% for FIT. Among the patients with totally negative results on colonoscopy, the specificity was 89.8% for the sDNA test and 96.4% for FIT (*P*<.001). The numbers of patients who would need to be screened to detect one cancer were 154 with colonoscopy, 166 with sDNA, and 208 with FIT.

CASE STUDY (CONTINUED): Recognizing that JS has limited knowledge about CRC, yet has strong concerns about colonoscopy, the primary care physician briefly highlights the epidemiology of CRC and the importance of early detection. He also lets JS know that there are several tests for screening and together they review the tests (**TABLE 3**) and decide what screening test JS is comfortable undergoing. In addition, and to help with patient education and compliance, he asks JS to read Colorectal Cancer Prevention and Early Detection published by the American Cancer Society as it discusses numerous issues regarding CRC screening, including details about the available tests.[2]

SUMMARY

Colorectal cancer is a generally slow-growing cancer that is highly curable when detected at an early, localized stage. Due to the lack of symptoms, even with advanced disease, screening is required to ensure cancers are detected early. Currently, however, only 3 in 5 people eligible for CRC screening undergo screening. Barriers vary somewhat by screening test and may differ in individual patients. Screening tests are generally more affordable due to recent changes in Medicare and private insurance coverage. Discussion with patients to identify barriers to screening makes it possible to select among the currently available invasive and noninvasive screening tests to determine the test that best meets the patient's health needs with the overall goal of increasing screening for a preventable disease. ●

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Individualizing Pharmacologic Management of Irritable Bowel Syndrome

Louis Kuritzky, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES:

1. Characterize the scope of problem in primary care
2. Implement recommended strategies for diagnostic testing
3. Compare the benefits and limitations of non-pharmacologic and pharmacologic therapy
4. Select evidence-based treatment

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and competency regarding primary care management of irritable bowel syndrome.

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SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium.

SUPPORTER

This activity is supported by an educational grant from Forest Laboratories, Inc. and Ironwood Pharmaceuticals.

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Release Date: 10 Dec 2015
Expiration Date: 9 Dec 2016

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SUPPORT

This CME article is sponsored by Primary Care Education Consortium and supported by funding from Forest Laboratories, Inc., and Ironwood Pharmaceuticals.

CASE STUDY. FB is a 31-year-old female who called the previous day for an appointment with her primary care physician (PCP). The PCP greets FB and says, "You were here 2 weeks ago for a follow-up visit for your asthma. Everything seemed to be okay then. Have you been having difficulties since I saw you?"

FB says "No, my asthma symptoms have been okay. I've wanted to talk with you for some time about something else. I've been having problems going to the bathroom, but there never seems to be time to discuss this when I see you. I just want these problems to go away."

INTRODUCTION

Epidemiology

The emotions expressed by this patient are not uncommon in patients with irritable bowel syndrome (IBS), whether their symptoms are constipation predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), or mixed (IBS-M).[1,2] A recent survey of people with mild/moderate IBS asked: "What is the most important thing your health care provider can do to maximize his/her relationship with you?" The topmost issue participants identified was, "I need more empathy and listening from my health care provider about how much IBS affects my life."[3]

The prevalence of IBS varies widely by geographic region and diagnostic criteria. The syndrome affects an estimated 12% of people in North America, with women at higher risk than men (relative risk 1.67).[4] IBS-D is the most common subtype of IBS (40% of diagnoses), compared with IBS-C (35%) and IBS-M (23%).[4] Comorbidities of IBS include pain hypersensitivity syndromes such as fibromyalgia, interstitial cystitis, migraine, chronic pelvic pain, and temporomandibular joint disorders.[5,6] IBS is associated with reduced work productivity and increased use of health-related resources.[7,8]

People with IBS experience significant morbidity, including lower self-esteem and overall poorer psychologic quality of life.[6] Physical quality of life has been reported to be the same as or worse than patients with diabetes, depression, or gastroesophageal reflux disease.[9] It has been reported that on average, people with IBS would sacrifice 10 to 15 years of their remaining life expectancy for an immediate cure.[10] IBS generally affects men and women similarly, although women may experience slightly greater severity of somatic symptoms and lower quality of life, the latter due to greater anxiety.[11,12] Women with IBS-D are particularly bothered by social concerns, and may resort to procedures like altering clothing, avoiding strenuous exercise, and avoiding activities they think might place them at risk of embarrassment (eg, having to frequently use the toilet during a long trip).[12]

DIAGNOSIS

The ill-defined pathogenesis of IBS, lack of a biomarker for the disease, and no universally agreed definition can make diagnosis challenging. Nonetheless, IBS is not a diagnosis of exclusion and is based on the signs and symptoms consistent with ROME III criteria, and the absence of signs indicative of other abdominal pathology.

A detailed history is the most important component of diagnosis. Physical examination is oriented to exclude other pathologies that could produce similar symptoms. When choosing therapy, it is critical to identify whether constipation, diarrhea, or mixed altered stool patterns predominate. The course of IBS is unpredictable since 35% to 50% of patients will demonstrate a chronically stable condition, other patients completely remit, and still others fluctuate between IBS categories and severity of symptoms.[13]

One widely recognized standard for the diagnosis of IBS is the Rome III criteria.[14] According to Rome III, IBS is defined by the presence of recurrent abdominal pain or discomfort at least 3 days/month in the past 3 months associated with 2 or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool.

To satisfy the Rome III criteria, symptom onset should occur at least 6 months before diagnosis.[15]

Patients for whom diagnostic testing is appropriate are those with alarm features such as age at onset older than 50 years, systemic signs (eg, unintentional weight loss, fever), nocturnal symptoms, family history of colon cancer, and any sign of bleeding (eg, anemia, rectal bleeding, positive fecal occult blood test, hematemesis). Symptoms of IBS-D and recent antibiotic use should prompt evaluation for *Clostridium difficile* colitis.[16] In the absence of alarm features, diagnostic testing provides no additional diagnostic certainty.[16-20] However, some experts recommend the performance of selected tests, such as complete blood count, C-reactive protein or fecal calprotectin, serologic testing for celiac disease, and age-appropriate screening for colorectal cancer, to exclude other organic diseases.[21]

Abdominal symptoms (eg, pain, discomfort, cramping, bloating) more commonly prompt patients to seek medical care than altered bowel habits (eg, urgency, loose/watery stools, frequency, straining).[22] The frequency and severity of bloating are similar or greater in people with IBS-C than IBS-D.[23,24] Individuals with IBS-D experience a greater decline in quality of life—they are more likely to alter their food intake and experience greater impact on daily activities and

TABLE 1 Summary of initial interventions for IBS[27]

Statement	Strength of recommendation	Quality of evidence
Specialized diets may improve symptoms in individual IBS patients.	Weak	Very low
Fiber provides overall symptom relief in IBS.	Weak	Moderate
Psyllium, but not bran, provides overall symptom relief in IBS (data presented for psyllium).	Weak	Moderate
There is no evidence that polyethylene glycol improves overall symptoms and pain in patients with IBS.	Weak	Very low
Certain antispasmodics provide symptomatic short-term relief in IBS. Adverse events are more common with antispasmodics than placebo.	Weak	Low
There is insufficient evidence to recommend loperamide for use in IBS.	Strong	Very low
There is insufficient evidence to recommend prebiotics or synbiotics in IBS.	Weak	Very low
Taken as a whole, probiotics improve global symptoms, bloating, and flatulence in IBS. Recommendations regarding individual species, preparations, or strains cannot be made at this time because of insufficient and conflicting data.	Weak	Low
Peppermint oil is superior to placebo in improving IBS symptoms. The risk of adverse events is no greater with peppermint oil than with placebo.	Weak	Moderate
A variety of psychological interventions are effective in improving IBS symptoms.	Weak	Very low

Abbreviations: IBS, irritable bowel syndrome.

relationships than those with IBS-C.[25] Bloating negatively impacts energy level and food intake, the latter particularly among women.[12,22] Compared with persons with minimal or mild bloating, persons with IBS and moderate to severe bloating report more daily symptoms of anxiety and depression, have more history of depressive disorders, and exhibit higher psychological distress.[26]

CASE STUDY (CONTINUED). The history shows that FB's bowel habits changed nearly 2 years ago when she began to experience abdominal bloating and occasional diarrhea. Since that time, her symptoms have increased and she now has abdominal discomfort 3 to 4 days per month. The pain is usually relieved with defecation. The frequency of her bowel movements has changed, and she now has more than 1 bowel movement on some days. FB also notes that she occasionally won't have a bowel movement for 3 to 4 days. Because FB has no alarm features for IBS, her PCP decides no further work-up is needed and makes a diagnosis of IBS-D based upon Rome III criteria.

TREATMENT

The overall management of a person with IBS emphasizes the importance of safety since IBS is not a fatal disease. However, because quality of life can be dramatically reduced, identifying and treating the symptoms that are most concerning to the patient is also a high priority.

CASE STUDY (CONTINUED). The PCP discusses some of the possible causes of IBS-D and asks her to review *IBS: A patient's guide to living with irritable bowel syndrome*, which was developed by the American Gastroenterological Association (www.gastro.org/patient-center/IBS_Brochure_Online.pdf).

The PCP assures FB that there are many treatment options for IBS and would like to begin with treatments that pose minimal safety concerns. She refers FB to a website that discusses low FODMAP (fermentable oligo-di-monosaccharides and polyols) diets to help her identify foods that might be causing her symptoms and to avoid or reduce eating those foods. FB is also advised to use an over-the-counter antidiarrheal, such as loperamide, for more severe symptoms. They also talk about situations that may be particularly stressful and how to handle them.

Initial therapy

Patients with IBS are frequently treated initially with self-care and other nonprescription interventions. While many of these treatments are supported by weak evidence, their safety supports their use as initial therapy (**TABLE 1**).[27-29] Soluble fiber (psyllium) appears to be more beneficial than insoluble fiber

TABLE 2 **Key safety considerations with selected prescription medications for IBS**

Medication (IBS subtype)	Contraindications	Warnings/pregnancy	Common adverse events
Lubiprostone[35] (women age ≥18 y with IBS-C)	• Known or suspected mechanical GI obstruction	• Avoid in severe diarrhea • Pregnancy category C	• Nausea • Diarrhea • Abdominal pain
Linaclotide[36] (IBS-C)	• Children ages <6 years • Known or suspected mechanical GI obstruction	• Avoid in children age 6-17 years • Pregnancy category C	• Diarrhea • Abdominal pain • Flatulence • Abdominal distension
Rifaximin[37] (IBS-D)	• History of hypersensitivity to rifaximin or rifamycin antimicrobial agents	• May cause *Clostridium difficile*-associated diarrhea • Caution in hepatic impairment (Child-Pugh Class C) • Avoid concomitant use with a P-glycoprotein inhibitor • Pregnancy category: Not categorized	• Increased alanine aminotransferase • Nausea
Eluxadoline[38] (IBS-D)	• Known or suspected biliary duct obstruction • Sphincter of Oddi disease or dysfunction • Alcohol abuse, drinks >3 alcoholic beverages/day • Pancreatitis, structural disease of pancreas • Hepatic impairment (Child-Pugh Class C) • Severe constipation or sequelae from constipation or known or suspected mechanical GI obstruction	• Sphincter of Oddi spasm and pancreatitis • Pregnancy category: Not categorized	• Constipation • Nausea • Abdominal pain
Alosetron[39] (Women with severe IBS-D)	• History of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, GI perforation, and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment • Concomitant use of fluvoxamine	• Infrequent GI AEs, eg., ischemic colitis and serious complications of constipation • Pregnancy category B	• Constipation • Abdominal discomfort and pain • Nausea • GI discomfort and pain

Abbreviations: AEs, adverse events; GI, gastrointestinal; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS.

(bran) in symptom improvement for all IBS, but may worsen bloating. Nonprescription medications for initial therapy include diphenoxylate/atropine and loperamide or other anticholinergics for IBS-D, and bisacodyl, docusate sodium, lactulose, polyethylene glycol 3350 for IBS-C.

A variety of psychological interventions, including cognitive behavioral therapy, have shown favorable results, and should be considered in patients who prefer such modalities or who do not respond to initial pharmacologic treatments.[30] The use of probiotics for IBS is supported by some evidence, generally showing benefit in improving overall symptoms and reducing abdominal pain, bloating, and flatulence. Benefits were primarily observed for combination products rather than individual probiotics.[31-34]

CASE STUDY (CONTINUED). At a 2-month follow-up, FB tells her PCP that she used a FODMAP reference to identify some foods to avoid and tracked her diet and symptoms since her last visit. She tried loperamide and reports less bloating as well as reduced stool frequency. She now experiences fewer days with more than 1 bowel movement and her pain and bloating are less severe.

FB and her PCP discuss further modifications to her diet and lifestyle. When her physician suggests psychological counseling, FB declines referral and asks if there is a medication that would help her.

Prescription medications

Prescription medications are second-line therapy in patients

TABLE 3 Summary of prescription medications for IBS[27]

Statement	Strength of recommendation	Quality of evidence
Alosetron is effective in females with IBS-D.	Weak	Moderate
Linaclotide is superior to placebo for the treatment of IBS-C.	Strong	High
Lubiprostone is superior to placebo for the treatment of IBS-C.	Strong	Moderate
Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D.	Weak	Moderate
Antidepressants (tricyclic antidepressants and SSRIs) are effective in symptom relief in IBS. Side effects are common and may limit patient tolerance.	Weak	High
Mixed 5-HT4 agonists/5-HT3 antagonists are not more effective than placebo at improving symptoms of IBS-C.	Strong	Low

Abbreviations: 5-HT3, serotonin subtype 3; 5-HT4, serotonin subtype 4; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; SSRI, selective serotonin reuptake inhibitor.

who do not achieve adequate relief of the predominant symptoms of IBS with initial therapy (eg, bloating, abdominal pain, constipation, diarrhea).[1] Safety remains a key consideration in selecting therapy (**TABLE 2,** previous page).[35-39] In addition to safety, treatment selection is guided by factors such as patient comorbidities, values, and preferences, as well as medication cost and insurance coverage. Since there are few high-quality, head-to-head studies, recommending a treatment hierarchy is difficult. Treatment selection may also be guided by the strength of recommendation and quality of evidence from a 2014 meta-analysis conducted by the American College of Gastroenterology (**TABLE 3**).[27]

The 2 newest prescription medications for IBS are rifaximin and eluxadoline, both approved by the FDA in May 2015. Rifaximin is a derivative of the antibacterial rifampin.[37] Gastrointestinal absorption of both eluxadoline and rifaximin is minimal.[37,38] Eluxadoline is a mu-opioid receptor agonist, as well as a delta-opioid receptor antagonist and a kappa-opioid receptor agonist.[38] A brief overview of these less familiar medications is provided below.

Rifaximin

The safety and efficacy of rifaximin for the treatment of IBS-D were established in 3 double-blind, placebo-controlled trials. The 2 TARGET trials utilized identical designs in which a total of 1258 patients with IBS, but excluding IBS-C, were randomly assigned to receive rifaximin 550 mg or placebo 3 times daily for 14 days.[40] Patients were then followed for an additional 10 weeks without further treatment. Every 2 weeks of the 12-week study, patients were asked if they had adequate relief of their IBS symptoms during the previous 7 days. Significantly more patients treated with rifaximin than placebo answered "yes" for at least 2 of the first 4 weeks after treatment (40.8% vs 31.2%, respectively, *P*=.01 in TARGET 1; 40.6% vs 32.2%, respectively, *P*=.03 in TARGET 2). Similarly, significantly more patients treated with rifaximin than placebo: (1) achieved adequate relief of IBS-related bloating for at least 2 of the first 4 weeks after treatment; (2) had relief of IBS-related abdominal pain and discomfort during the primary evaluation period; and (3) had adequate relief of global IBS symptoms within the first month, with continued relief during the first 2 months and during all 3 months in both studies. Over the 12 weeks, the incidences of adverse events and serious adverse events were similar in the rifaximin and placebo groups.

A third study evaluated repeat treatment for up to 46 weeks.[37] The first phase was a 14-day open-label period, with responders followed for up to 20 treatment-free weeks. Responders had defined improvements in weekly average abdominal pain scores and stool consistency. Those who experienced a recurrence were randomized to rifaximin 550 mg or placebo three times per day (N=636) for two additional 14-day repeat treatment courses separated by 10 weeks. More patients treated with rifaximin than placebo were responders (reduced abdominal pain and improved stool consistency) in this final phase of the study.[37]

Eluxadoline

Two clinical trials of eluxadoline included a total of 2425 patients who met Rome III criteria for IBS-D with abdominal pain >3.0/10 and daily stool consistency score (Bristol Stool Scale) ≥5.5 and ≥5 on at least 5 days during the week prior to randomization.[38] Both clinical trials lasted 26 weeks; one had a 26-week extension followed by a 2-week follow-up, while the other included a 4-week placebo-withdrawal period following completion of the 26 weeks. Patients were randomized to 75 or 100 mg of eluxadoline or placebo twice daily. Efficacy was evaluated using an overall composite responder endpoint (simultaneous improvement of worst abdominal

pain by ≥30% and Bristol Stool Score <5 on the same day for ≥50% of days over the interval).[38]

In both studies, the proportion of patients who were composite responders to eluxadoline over 12 weeks was significantly higher compared with placebo for both doses. The proportion did not differ by sex. The composite response rates over 26 weeks were similar to placebo. During the 4-week withdrawal period in the second study, no evidence of worsening diarrhea or abdominal pain compared to baseline was demonstrated at either dose.[38]

SUMMARY

Irritable bowel syndrome is a common gastrointestinal disorder with constipation, diarrhea, and mixed subtypes. The diagnosis is generally based on a detailed history utilizing the Rome III criteria. Alarm signals necessitate more extensive diagnostic evaluation. Nonpharmacologic options and over-the-counter remedies (eg, loperamide) might not be supported by strong evidence, but are often chosen as initial treatment for their safety and tolerability. Psychological interventions may be beneficial. Newer pharmacologic agents such as alosetron, eluxadoline, linaclotide, lubiprostone, and rifaximin are supported by higher quality evidence than older agents such as antispasmodics and laxatives.

Patients with IBS commonly report that clinicians offer insufficient empathy and validation of their symptoms. Physicians therefore should strive to improve communication methods that specifically provide such reassurance. Individualizing treatment based on patient values and preferences is essential. ●

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Familial Hypercholesterolemia in Youth

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OBJECTIVES

- Summarize current US clinical guidelines for the management of familial hypercholesterolemia in youth (children and adolescents) and contrast them with guidelines for adults.
- Identify strategies for screening and treatment of inherited lipid disorders in youth associated with an increased risk of premature atherosclerotic cardiovascular disease (ASCVD).
- Educate providers on the need for therapeutic lifestyle changes and the appropriate use of lipid-modifying therapies in high-risk youth.

INTRODUCTION

Familial hypercholesterolemia (FH) is a group of genetic defects resulting in severe elevation of atherogenic blood cholesterol levels and high risk for premature atherosclerotic cardiovascular disease (ASCVD).[1-5] The increase in low-density lipoprotein cholesterol (LDL-C) associated with FH is a concern because increased LDL-C, as well as increased non–high-density lipoprotein cholesterol (non–HDL-C), in youth is strongly correlated with accelerated atherosclerosis.[4-9] Atherosclerosis associated with FH begins in childhood, as evidenced by the presence of fatty streaks and fibrous plaques in coronary arteries found on autopsy.[6,7,10,11] Autopsy data from the Bogalusa Heart Study showed that while fatty streaks were very common, 8% of children ages 2 to 15 years and 34% of 16- to 20-year-olds had fibrous plaque lesions, precursors of more advanced atherosclerotic lesions, in their coronary arteries.[6] The extent of fatty streak and fibrous plaque lesions in the coronary arteries and aorta together was strongly associated with increased LDL-C, as well as other risk factors such as elevated body mass index and systolic blood pressure.

Additional evidence of the adverse effects of risk factors in adolescents, specifically increased LDL-C, includes significantly increased abdominal aortic and carotid intima-media thickness (CIMT) and impaired endothelial function.[12-15]

EPIDEMIOLOGY AND ETIOLOGY

Familial hypercholesterolemia, one type of autosomal dominant hypercholesterolemia, is classified as either heterozygous or homozygous. Recent data demonstrate that the prevalence of heterozygous FH (HeFH) is almost 2 times higher than previous estimates, making it by far the most common inherited metabolic disorder, with an estimated prevalence of 1 in 200 to 250 among some Caucasian populations and ~1 in 500 overall.[1,16] The prevalence of HeFH is higher in founder populations, ie, a small number of people from a larger population who establish a new population, which may result in loss of genetic variation. Founder populations with a higher prevalence of HeFH are people of French Canadian, South African Afrikaner, Jewish, Indian, Tunisian, Christian Lebanese, Icelandic, and Finnish descent.[17] If left untreated, fatal or nonfatal coronary events occur in approximately 50% of men before age 50 years and 30% of women before age 60 years.[4] In those with HeFH under 40 years of age, the relative risk for a nonfatal cardiac event is 100-fold greater than that for the general population.[2] Both the 2011 National Heart, Lung, and Blood Institute (NHLBI) pediatric guidelines[18] and

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DISCLOSURES

Dr. McNeal discloses that she is an employee of Baylor Scott & White Health and is an officer of the National Lipid Association.

Dr. Toth discloses that he is on the speakers' bureau for Amarin Corporation, AstraZeneca; GlaxoSmithKline; Kowa Pharmaceuticals America, Inc.; Merck & Co., Inc.; and is a consultant for Aegerion Pharmaceuticals, Inc.; Amgen Inc.; AstraZeneca; Kowa Pharmaceuticals America, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; and Sanofi US with Regeneron Pharmaceuticals.

Dr. Wilson discloses that he is on the advisory board for Aegerion Pharmaceuticals, Inc., and the speakers' bureaus for Osler Institute and Synageva BioPharma Corp. He does contracted research for Merck Sharp & Dohme Corp. and Novo Nordisk Inc.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from AstraZeneca.

the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) adult guidelines[19] use an LDL-C cut point of >190 mg/dL (>4.9 mmol/L) to identify a high-risk phenotype likely associated with a genetic defect in cholesterol metabolism, including the classic monogenic defects.[4] However, FH should be suspected in untreated youth with an LDL-C level >160 mg/dL (>4.1 mmol/L) or a non–HDL-C level >190 mg/dL (>4.9 mmol/L) and in adults with an LDL-C level >190 mg/dL (>4.9 mmol/L) or a non–HDL-C level >220 mg/dL (>5.7 mmol/L).[20-22]

Homozygous FH (HoFH) is less prevalent, occurring in ~1 in 1 million persons; the untreated LDL-C level is typically >500 mg/dL (>13 mmol/L).[2,16,23] Persons with HoFH develop CHD very early in life and, if untreated, can die before age 20 years.[16]

Familial hypercholesterolemia is commonly attributed to autosomal dominant inherited defects in the LDL receptor (LDLR) that cause impaired uptake and metabolism of LDL particles by hepatocytes. There are more than 1,600 known mutations of the LDLR gene, accounting for 85% to 90% of FH cases.[3] Familial hypercholesterolemia also includes defects in the genes for: (1) apolipoprotein (Apo) B, which leads to reduced affinity of LDL particles for the LDLR; (2) gain-of-function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9) that promote increased proteolytic destruction of the LDLR, thereby reducing LDL clearance capacity[2,3]; and (3) defective forms of adaptor protein-1, a rare autosomal recessive disorder, which helps to align the LDL particle-LDLR complex in clathrin-coated pits.[24]

GUIDELINE RECOMMENDATIONS FOR THE MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLEMIA IN YOUTH

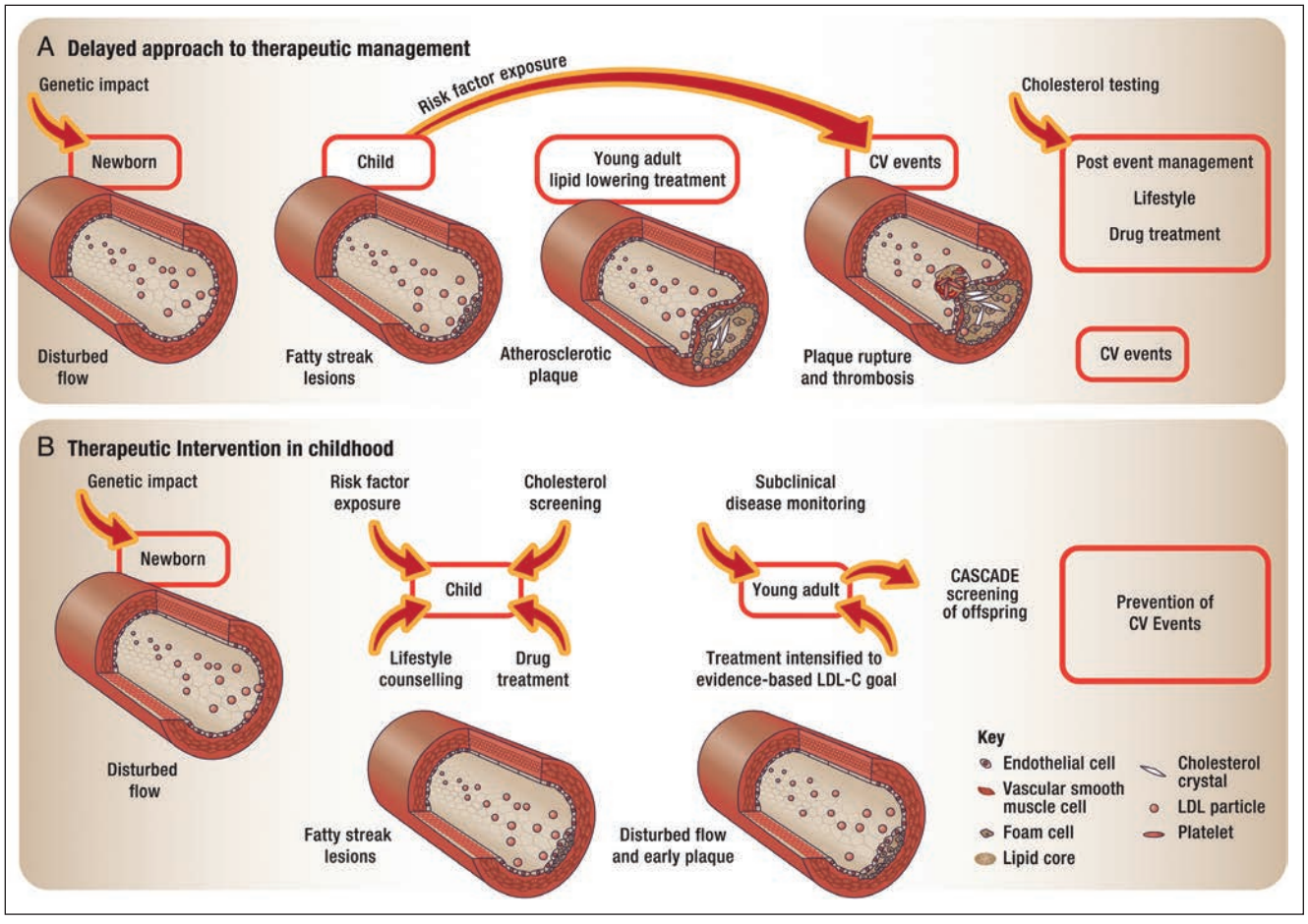
The overall management of youth with FH centers on early identification, so that appropriate management is initiated as early as possible in families with this disease. Given the autosomal dominant inheritance, there is a 50% chance that an affected parent will pass on the gene to his or her child, or conversely, if an affected child is identified, one of the parents will be affected. The focus of early management is on strategies aimed at preventing the acquisition of other risk factors, including adverse lifestyle habits. Current evidence suggests that HeFH is vastly underdiagnosed in youth and in adults.[5,16] This is due, in part, to the relatively uncommon outward physical findings and/or symptoms of CHD in youth and young adults. Oftentimes, treatment is not initiated until adults are diagnosed with CHD.[16] If guidelines for FH diagnosis and treatment in youth were followed, it is estimated that the onset of CHD could be delayed by almost 20 years, ie, from age 35 to age 53 years, resulting in substantial benefits with respect to adult mortality and morbidity.[16] The paradigm of shifting from treating FH once CHD is diagnosed to early detection and interventions to delay the onset of CHD and/or decrease the severity of disease, is well represented in the **FIGURE**.[1] Family medicine providers are uniquely positioned to play an important role in appropriate family screening and management across all age groups.

Screening

In 2011, the NHLBI published the "Summary Report of the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents."[18] These evidence-based guidelines provide detailed recommendations by risk factor with supportive actions to facilitate implementation. Risk factors include lipid profile, family history of early cardiovascular disease, diabetes, and others. The recommendations are summarized in a cardiovascular health schedule by age group from birth through 21 years of age and 8 risk factors. These guidelines advocate a more aggressive approach to screening for FH than earlier guidelines (**TABLE 1**).[18,19,25-30] Similar to prior recommendations in the pediatric population, including the 1992 National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents,[25] the 2006 AHA[26] and the 2008 American Academy of Pediatrics (AAP)[27] guidelines, the 2011 NHLBI and 2015 NLA guidelines recommend that lipid screening begin any time after age 2 years in selected high-risk youth.[18,30] High-risk youth include those likely to have FH or another inherited atherogenic dyslipidemia based on family history, including a history of premature ASCVD or hyperlipidemia in first- or second-degree relatives, and/or in youth with multiple risk factors or risk conditions (the latter discussed below). A fasting lipid profile in these youth was recommended as the initial screening test.

A key and controversial difference among the prior and current pediatric guidelines concerns the recommendation for universal lipid screening once in children ages 9 to 11 years and once again at ages 17 to 21 years.[18,31] In these age groups, the guidelines also diverged from prior recommendations by suggesting that a nonfasting lipid profile with a calculated non–HDL-C could be used as the initial screening test instead of a fasting lipid profile. The basis for recommending lipid screening in all children aged 9 to 11 years is that (1) this is a developmental stage when lipid levels are stable and more likely to predict future adult lipid levels, compared with puberty, when lipid levels can fall by as much as 10% to 20%; and (2) because selective screening based on family history identified only a small percentage of high-risk youth.[18] To the best of our knowledge, the United States is the only country to recommend universal lipid screening in youth, except for Slovenia.[32] However, multiple countries have implemented

FIGURE **Impact of early vs delayed intervention in the development of early atherosclerotic vascular disease in familial hypercholesterolemia**



The figure demonstrates the potential of early recognition of FH, combined with treatment from a young age, to substantially delay atherosclerosis progression.

Wiegman A, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J*. 2015;36(36):2425-2437 by permission of European Society of Cardiology.

targeted screening programs using "cascade" screening, ie, identifying and testing relatives of individuals affected by a genetic disease.[16]

As noted above, and to facilitate lipid screening, providers are encouraged to order a nonfasting lipid panel as the initial screening test, which allows calculation of non–HDL-C (defined as total cholesterol minus HDL-C). Non–HDL-C reflects the sum of all atherogenic lipoproteins and is superior to LDL-C as a predictor of ASCVD in the adult population.[9] Non–HDL-C can be accurately calculated in a nonfasting state, which may facilitate opportunistic testing in school-aged youth. If the nonfasting non–HDL-C is ≥145 mg/dL and/or the HDL-C is <40 mg/dL, the average of 2 subsequent fasting lipid profiles is recommended before determining the most appropriate treatment plan.[18,31]

Another concept unique to the pediatric population was introduced in the 2006 AHA pediatric guidelines[26] and carried forward in subsequent recommendations. This was the identification of conditions that are "accelerators to the atherosclerotic process." The conditions are stratified as high and moderate risk and include chronic kidney disease, chronic inflammatory diseases, Kawasaki disease, orthotopic heart transplant, and cancer, among others. Awareness of these conditions and additional risk factors, which are summarized in **TABLE 2,** is important to guide the need for therapeutic interventions described in the guidelines.[18]

Cascade screening and reverse cascade screening

The largely autosomal dominant nature of FH provides an opportunity to identify previously undiagnosed individuals

TABLE 1 Guideline comparison for lipid screening

	NCEP 1992[25]	AHA 2006[26] AAP 2008[27]	AAFP[41] USPSTF 2007[43]	NCEP ATP III and Update[28,29]	NHLBI 2011[18]	AHA/ACC 2013[19]	NLA 2015[30]
Screened population	Youth with: • A positive or unknown family history • Other major risk factors present	Youth with: • A positive or unknown family history • Other major risk factors present	• Men age ≥35 y or 20-35 y if increased risk for CHD • Women age ≥20 y with increased risk of CHD	Universal screening for all adults age ≥20 y	Targeted screening and universal screening	Assess traditional ASCVD risk factors every 4 to 6 y in adults age 20-79 y who are free from ASCVD; estimate 10-y ASCVD risk every 4 to 6 y in adults 40-79 y of age who are free from ASCVD[a]	Targeted screening and universal screening
First screen	Any time >2 y of age	Any time >2 y of age	Any time >20 y if increased risk of CHD; otherwise ≥35 y (men)	Age 20 y	Any time ≥2 y of age (targeted screening) Age 9 to 11 y and 17 to 21 y (universal screening)	Age 20 y if not previously screened	Any time ≥2 y of age (targeted screening) Age 9 to 11 y and 20 y or earlier if dyslipidemia present (universal screening)

[a]The guideline also notes the importance of screening family members of those with a low-density lipoprotein cholesterol ≥190 mg/dL.

Abbreviations: AAFP, American Academy of Family Physicians; AAP, American Academy of Pediatrics; ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; NCEP, National Cholesterol Education Program; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NHLBI, National Heart, Lung, and Blood Institute; NLA, National Lipid Association; USPSTF, United States Preventive Services Task Force.

from a person diagnosed with FH (ie, an index case) through the use of cascade screening. Cascade screening involves testing lipid levels in all first-degree relatives of the index case. As additional individuals with FH are identified, their first-degree relatives should also be tested. Cascade screening is cost-effective in terms of cost per year of life saved, because it allows early diagnosis and early intervention.[33] Although genetic screening programs are widely used in Europe, lipid screening alone may be potentially more cost-effective, at least in the US population, especially given that many individuals with severely elevated LDL-C >190 mg/dL may not have defects in genes that are commonly screened and may instead have multiple genetic defects that give rise to lifelong elevations of cholesterol and a comparable consequent risk of ASCVD.[4,34] Therefore, in the United States, cascade screening for FH (or other forms of autosomal dominant hypercholesterolemia) is based on the phenotype of a high LDL-C rather than genotyping.[20,35]

Although arguments against universal lipid screening in youth include the fact that it may not prove to be cost-effective, this may be offset because it has the potential to detect FH in the parent(s) of affected youth.[36] Among these children, the parent with the higher cholesterol level has a 96% chance of having FH.[37] In actuality, and given that 99% of the US population with FH remains undiagnosed,[16] opportunistic screening employing both cascade screening and "reverse cascade screening" (ie, testing relatives of affected youth) may be the best approach to identify the highest number of affected individuals.

Comparison with other professional societies and with adult screening guidelines

The 2011 NHLBI screening recommendations are similar to the 2011 and 2015 recommendations by the National Lipid Association (US), which call for targeted screening in children ages 2 years and older with a family history of premature ASCVD or elevated cholesterol, and universal screening in children ages 9 to 11 years.[18,23,30,31] While some professional societies outside of the United States recommend targeted or cascade screening, none have endorsed universal screening in children.[1,16,38-40] These disparate approaches to screening are also likely a reflection of vastly different health care sys-

TABLE 2 Conditions for targeted screening in children 2 years of age and older[18]

Recommendation
Measure fasting lipid profile twice[a]; average results if: • Parent, grandparent, aunt/uncle, or sibling with MI, angina, stroke, CABG/stent/angioplasty at age <55 y in men or <65 y in women • Parent with (untreated) total cholesterol ≥240 mg/dL or known dyslipidemia • Child has diabetes, hypertension, BMI ≥95th percentile[b] or smokes cigarettes • Child has a moderate- or high-risk medical condition[c,d]

[a]Interval between fasting lipid profile measurements: after 2 weeks but within 3 months.

[b]BMI ≥85th percentile if age 12-16 y.

[c]Moderate-risk medical condition: Kawasaki disease with regressed coronary aneurysms, chronic inflammatory disease (systemic lupus erythematosus, juvenile rheumatoid arthritis), human immunodeficiency virus infection, nephrotic syndrome.

[d]High-risk medical condition: type 1 diabetes mellitus, type 2 diabetes mellitus, chronic kidney disease/end-stage renal disease/post-renal transplant, post-orthotopic heart transplant, Kawasaki disease with current aneurysms.

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; MI, myocardial infarction.

tems and health care insurance coverage. In their September 2015 Summary of Recommendations for Clinical Preventive Services, the American Academy of Family Physicians reaffirmed their previous recommendations to follow the US Preventive Services Task Force 2007 recommendations, finding that there was insufficient evidence to recommend for or against routine lipid screening in youth and young adults younger than age 20 years.[41]

In contrast to the harmonized guidelines for diabetes management,[42] the pediatric and adult lipid guidelines remain discordant with respect to both the screening and treatment of dyslipidemia. Adult and pediatric lipid screening guidelines are summarized in **TABLE 1**. Lipid screening is recommended for adults age 20 years and older, except in the US Preventive Services Task Force 2008 guidelines, which suggest screening men 35 years of age and older and women 45 years of age and older.[43]

Diagnosis

There is no single universally accepted criterion for the diagnosis of FH. FH should be suspected in youth and in adults when the untreated fasting LDL-C is ≥190 mg/dL or ≥160 mg/dL if there is a family history of premature ASCVD or hypercholesterolemia in a parent.[1,5,16,35] By itself, an LDL-C ≥190 mg/dL in individuals younger than 20 years of age is associated with an 80% probability of FH.[23]

Multiple diagnostic criteria for FH have been developed, and several can be applied to youth, including those specified by the FH Foundation, the Simon-Broome criteria,[1,44] and the US Make Early Diagnosis—Prevent Early Death (MED—PED).[20] However, there are substantial problems in trying to apply these criteria in primary care. Notably, results of genetic testing and a comprehensive family history including the age of relatives affected by CHD and/or untreated lipid levels in first-, second-, or third-degree relatives are rarely available, may be inaccurate, or may be amplified by the effects of a high-fat diet.

The physical signs of FH are rare in youth in all but the most severe forms of HeFH and in those with HoFH. However, if present, the signs confirm the diagnosis. These include the classic tendon xanthomas or thickening, especially involving the Achilles tendon and finger extensor tendons, xanthelasma, tuberous xanthomas, and corneal arcus (partial or complete).[4] The clinical diagnosis is highly probable when other children with FH in the family are identified, or when the patient or a first- or second-degree relative exhibits these findings.[23] Other findings may include murmurs associated with aortic valve stenosis as well as carotid and femoral bruits secondary to peripheral vascular disease.

Genetic testing is generally not needed for diagnosis or clinical management and does not rule out FH. Identifying a phenotype consistent with FH is adequate for diagnosis, ie, an untreated LDL-C level in the child consistent with FH plus a family history of premature CHD, and/or an untreated cholesterol level in a parent consistent with FH.[1,20,45] Wald et al demonstrated that cholesterol screening to detect FH earlier in life (ages 1 to 2 years) is in close agreement with gene testing results and is associated with few false positives because of the negligible effect of diet at this age. This is in contrast to screening later in adolescence or in adults.[46]

Treatment

The very high lifetime risk of ASCVD, including premature onset of CHD, in youth with FH is clearly associated with a

need for early and aggressive lifestyle modification and careful screening to detect the development of other risk factors that accelerate atherosclerosis. Most concerning in the pediatric population is the development of risk factors attributable to overweight/obesity and the associated metabolic sequelae, especially a low HDL-C in youth with FH. The extent to which this "perfect storm of risk factors" will affect the age of onset of CHD is unknown. For youth with an LDL-C consistent with FH (ie, >190 mg/dL), the treatment goal is lowering the LDL-C to <130 mg/dL (95th percentile) or at least to achieve a ≥50% reduction in LDL-C.[18,31] The latter goal is consistent with the most recent adult treatment guidelines for adults with FH.[19] Youth with FH and additional ASCVD risk factors (eg, obesity, hypertension, diabetes mellitus, and high- or moderate-risk conditions) may benefit from more aggressive LDL-C goals.[31]

Lifestyle modification

The 2011 pediatric guidelines have been criticized for promoting lipid-lowering medications in youth without FH but with a moderately elevated LDL-C in combination with other risk factors.[47] However, a cornerstone of the treatment guidelines focuses on the importance of preventing or improving unhealthy lifestyle habits that can accelerate atherosclerosis. A benefit of selective screening early in life in high-risk youth, ie, after 2 years of age, is that it provides a window of opportunity to positively impact lifestyle habits in the family before adverse habits become firmly entrenched, which typically occurs by early adolescence. All families affected by FH should be encouraged to adopt a healthy lifestyle, including avoidance of tobacco products, a healthy diet, and regular physical activity. The guidelines provide detailed descriptions for a Cardiovascular Health Integrated Lifestyle Diet (CHILD)-1 and a more intensified CHILD-2-LDL diet that should consist of 25% to 30% of calories from fat, ≤7% from saturated fat, ~10% from monounsaturated fat, and <200 mg/day of cholesterol, while avoiding trans fats as much as possible. Physical activity should consist of 1 hour/day of moderate to vigorous activity, while limiting sedentary time, including screen time (television, computer, etc), to <2 hours per day.[18,31]

Pharmacologic therapy

Although lifestyle modifications may reduce LDL-C by 10% to 15%, lipid-lowering drug therapy is almost always required to normalize the LDL-C level. The pediatric guidelines suggest that pharmacologic therapy should not generally be initiated before the age of 8 to 10 years in youth with HeFH.[18,30,31] Data from a large number of statin trials in middle-aged adults have clearly shown that the more LDL-C is lowered, the lower the risk of ASCVD events. Conversely, estimates from the Framingham Offspring study also find that a longer exposure to a moderately elevated non–HDL-C resulted in an almost 4-fold increased rate of CHD.[48] In lieu of a placebo-controlled clinical trial spanning multiple decades, evidence from Mendelian randomization studies has been used to estimate the effect of lifelong exposure to lower LDL-C attributable to gene defects compared with pharmacologic lowering of LDL-C later in life. Using data from a meta-analysis of 26 (adult) statin trials and meta-analyses of combined data from Mendelian randomization studies, Ference et al reported up to a 3-fold greater reduction (on a log-scale) for genetically low LDL-C compared with treatment with a statin started later in life.[49] Also considering data from individuals with lifelong low LDL-C levels due to loss-of-function genetic variants in PCSK9, it suggests that the earlier and the longer LDL-C levels are reduced in youth and young adults with severe hypercholesterolemia, the lower their risk will be of future ASCVD events.[1]

The 2011 and prior pediatric guidelines note that the LDL-C level at which pharmacologic therapy can be initiated depends on a knowledge of family history and other risk factors and risk conditions. For example, the 2011 NHLBI guidelines recommend pharmacologic therapy for children ages 10 years and older if the LDL-C is ≥190 mg/dL despite 6 months of lifestyle modification. The LDL-C level for initiating pharmacologic therapy is lowered to ≥160 mg/dL if the child has a positive family history of premature CVD/events in first-degree relatives or ≥1 high-level risk factor/risk condition or ≥2 moderate-level risk factors/risk conditions.[18] Children younger than 8 to 10 years should generally not be treated with lipid-lowering medications unless they have HoFH or have other high-risk conditions.[1,18,30]

In addition to a healthy lifestyle, a low-dose statin is recommended as initial pharmacologic therapy in children and adolescents with FH based upon a history of efficacy, safety, and tolerability.[1,18,30,50] Randomized clinical trials in children and adolescents with FH have demonstrated LDL-C reductions similar to those in adults.[51-60] The longest trial to date includes data from youth with HeFH receiving pravastatin (20–40 mg/day) followed for a 10-year period.[61] No serious adverse effects were reported, and the carotid intima-media thickness was comparable to that of unaffected siblings. Results of the CHARON study showed similar benefits with rosuvastatin in the carotid intima-media thickness over a 2-year period.[60] Several meta-analyses of randomized controlled trials in children with FH have also shown no adverse effects on growth, development, or sexual maturation with statins. They also found that elevations in hepatic enzymes and muscle toxicity were similar to those with placebo.[58,62,63] Nonetheless, routine monitoring of hepatic enzymes and

TABLE 3 Approved lipid-lowering prescription medications in youth

	Heterozygous FH		
	Age	**Initial Dose**	**Maximum Total Daily Dose**
STATINS[a]			
Atorvastatin[68]	10–17 y	10 mg QD	20 mg
Fluvastatin[69]	10–16 y	20 mg QD	80 mg
Lovastatin[70]	10–17 y	10 mg QD	40 mg
Pitavastatin[71]	—	—	—
Pravastatin[72]	≥8 y	8-13 y: 20 mg QD 14-18 y: 40 mg QD	8–13 y: 20 mg 14–18 y: 40 mg
Rosuvastatin[73]	10–17 y	5 mg QD	20 mg
Simvastatin[74]	10–17 y	10 mg QD	40 mg
NON-STATINS[b]			
Colesevelam[75]	10–17 y	3750 mg/day	3750 mg
Ezetimibe[76]	10–17 y	10 mg QD	10 mg
Ezetimibe with atorvastatin[77]	Safety and effectiveness have not been established in pediatric patients.	10/10 to 10/20 mg/day	10/80 mg
Ezetimibe with simvastatin[78]	10–17 y	10/10 to 10/20 mg/day	10/40 mg

[a]After failing an adequate trial of diet therapy.

[b]As adjunctive therapy to diet.

Abbreviations: FH, familial hypercholesterolemia; QD, once daily.

clinical assessment for muscle toxicity are strongly recommended for children and adolescents on statins.[1,18]

There are unresolved questions regarding the long-term use of statins in youth, including long-term outcomes, safety, and cost-effectiveness, that require further evaluation, but the benefit of lifelong low LDL-C levels based on data from individuals with genetically low LDL-C emphasizes the importance of identifying high-risk youth early in life.[1] Arguments against the use of lipid-lowering medications have also been focused on the potentially indiscriminate use in youth without FH but with multiple moderate risk factors.[64] It is in the latter instance that the pediatric guidelines sharply diverge from treatment guidelines in young adults.[19,41,65] A recent estimate suggested that application of the pediatric guidelines in youth ages 17 to 21 years would result in a 6-fold increase in the number eligible for statin therapy compared with the 2013 ACC/AHA adult treatment guidelines.[66] Mounting data from Mendelian randomization studies provide important evidence with respect to the timing of FH diagnosis, the timing of initial treatment, and the potential benefits of lifelong lower atherogenic cholesterol levels (**FIGURE**). Although there is concern about the paucity of data for lifelong lipid-lowering therapies beginning in youth, there is little doubt that a markedly elevated LDL-C is causal in magnifying risk for ASCVD and leading to the well-characterized natural history of untreated FH.

Recommendations for pharmacologic therapy

Initiating pharmacologic therapy in youth ages 10 years and older with HeFH using a low-dose statin is recommended by the NHLBI 2011 guidelines, which were endorsed by the American Academy of Pediatrics[18,67]; age 8 years is recommended by the National Lipid Association.[30] All statins (except pitavastatin) are approved to treat children with HeFH who have failed an adequate trial of diet therapy (**TABLE 3**).[68-78] For youth who do not reach their target LDL-C level after at least 3 months on statins, the dose should be increased or, alternatively, ezetimibe, a bile acid sequestrant, or niacin may be initiated.[18] However, tolerability in children is a concern with a bile acid sequestrant and niacin. Referral to a lipid specialist may be considered in these cases.

Although evidence of benefit from clinical trials is lacking, treatment with lipid-lowering medications (ie, statins and ezetimibe) is recommended in youth with HoFH at diagnosis to reduce the risk of fatal CHD events before adulthood.[1,5] This should be followed by LDL apheresis as soon as possible. Liver transplantation and new biologic therapies, including the PCSK9 monoclonal antibodies, are also therapeutic options.

SUMMARY

Worldwide, guidelines support early identification, aggressive lifestyle management, and pharmacologic lipid-lowering therapies when appropriate in youth with FH. These guidelines are aimed at improving the unending cycle of premature CHD in families despite the vast body of knowledge regarding the natural history of undiagnosed and untreated FH. Although valid concerns have been raised about treating youth other than those with FH with lipid-lowering pharmaceuticals, we believe the preponderance of the evidence laid forth by multiple professional societies from the United States and abroad is clearly weighted in favor of early diagnosis and treatment with lifestyle modification, to prevent the acquisition of other risk factors, and habituation to lifelong low-fat diet and adequate physical activity. We can think of no other instance where providers in the field of family medicine could have such a profound impact on the current and future health of child and parent and even future generations. ●

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Update on the Recognition and Management of Gout: More Than the Great Toe

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INTRODUCTION

Gout is a rheumatic disease resulting from chronic deposition of uric acid crystals as monosodium urate (MSU) in tissues and joints causing joint pain and swelling that, over time, may result in permanent bone and joint damage. In humans, uric acid is the end product of purine metabolism given the evolutionary loss of the hepatic enzyme uricase.[1] This loss of uricase and the consequential higher serum uric acid (sUA) levels observed in humans may contribute to the development of this disease in individuals.

RISK FACTORS

Men are 3 times more likely than premenopausal women to suffer from gout, with prevalences of 5.9% and 2% of US adults, respectively. After menopause, the prevalence in women approaches that of men.[2] Hyperuricemia (sUA >6.8 mg/dL) is the most important risk factor for the development of gout. However, not all individuals with hyperuricemia experience symptoms of gout; conversely, 11% to 49% of people with gout have a normal sUA level.[3] Although 21.5% of US adults have hyperuricemia, only 3.9% are diagnosed with gout, thus only 1 in 5 people with hyperuricemia develop symptoms of gout.[2] This suggests that additional factors, such as genetic disposition, may increase the risk of gout.

In 80% to 90% of patients with gout, hyperuricemia results from impaired renal elimination of uric acid.[4,5] The kidney is responsible for the majority of uric acid excretion, which is largely controlled by a family of urate transporters. Mutations of transporters such as URAT1 and GLUT9 are associated with increased sUA levels.[6] Dietary factors such as consumption of purine-rich foods (red meat, seafood, visceral organs), and foods and drinks high in fructose contribute to the risk of developing gout. Moderate to heavy intake of alcohol, particularly beer (including "lite" beer and nonalcoholic beer since they are all high in the purine, guanosine) and hard liquor, also increase the risk of gout.[7] Some medications such as diuretics, low-dose aspirin (up to 325 mg/d), cyclosporine, niacin, pyrazinamide, and ethambutol are associated with an increased risk of gout.[8]

Patients with gout often have comorbid hypertension, diabetes mellitus, obesity, hypertriglyceridemia, hypercholesterolemia, chronic kidney disease, congestive heart failure, obstructive sleep apnea, and cardiovascular disorders (myocardial infarction, stroke, and peripheral artery disease).[8-16] However, the relationships of those diseases with gout and hyperuricemia are unknown.

DIAGNOSIS

An acute gout attack or an acute gout flare typically manifests within hours as a joint that is red, hot, swollen, and extremely tender to touch or movement. During the early course of the disease, untreated acute gout flares resolve over 7 to 10 days. Symptoms are typically limited to 1 joint early in the disease, with multiple joints possibly being affected as the disease progresses. Initially, men are more likely to experience symptoms in the big toe (podagra), while the elbow, wrist, and hands are more likely to be affected in women. In conjunction with other features, these signs and symptoms and disease patterns have been used to make a presumptive clinical diagnosis of gout. Other features that clinically make one more suspicious that the joint pain is due to gout include soft tissue lesions suggesting tophi, presence of associated comorbidities, family history of gout, and patient history of urolithiasis.

Five schemes for classifying gout have been developed since the 1960s, each with shortcomings that limit applicability to current practice.[17] Janssens et al developed a diagnostic rule for acute gout for use in primary care that includes 7 variables but does not require joint fluid analysis.[18] The 7 variables are: male sex, previous patient-

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DISCLOSURES

Dr. Doghramji discloses that he is on the advisory board for AstraZeneca; Merck & Co, Inc; and Teva Pharmaceuticals USA; and on the speakers' bureaus for Merck & Co, Inc; Takeda Pharmaceuticals U.S.A., Inc.; and Teva Pharmaceuticals USA.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from AstraZeneca.

reported arthritis attack, onset within 1 day, joint redness, first metatarsophalangeal joint involvement, hypertension or 1 or more cardiovascular diseases, and sUA >5.88 mg/dL. Using the criteria, the diagnostic validity of family physician diagnosis of acute gout has been found to be moderate with positive and negative predictive values of 0.64 and 0.87, respectively. The diagnostic rule is limited to patients with only 1 affected joint.[17]

Differentiating gout from other diseases that cause joint pain is important as it can alter prognosis and treatment. Although joint aspiration is definitive, the general absence of fever, rash, or other signs of systemic illness during an acute gout flare early in the course of the disease helps differentiate gout from septic arthritis. The diagnostic rule developed by Janssens et al has been shown by Lee et al to discriminate acute gout from septic arthritis.[18,19] Also, the incidence of septic arthritis is substantially lower than gout, and primarily occurs in sick, hospitalized patients who are possibly septic.

Hyperuricemia alone is not adequate to confirm the diagnosis of gout because of its lack of specificity for gout and lack of sensitivity during acute gout flares.[9,20] Aspiration of the joint or tophus and demonstrating MSU crystals with polarizing microscopy is highly sensitive and specific for the diagnosis of gout and is the gold standard.[9,21] While aspirating a joint that is swollen and painful may seem undesirable by both patient and clinician, since local anesthetic is used, this procedure actually leads to immediate pain relief in most patients with gout. And if corticosteroids are co-administered, relief can continue and be lasting. Radiography may not be useful in confirming the diagnosis in early or acute gout, but can show erosive or tophaceous changes in chronic gout.[9] Currently, an imaging method for early detection and confirmation of gout is ultrasonography where a characteristic finding of the double contour sign representing MSU deposition lining the synovial joints or microscopic tophi may be visualized, even in joints that have never had a flare.[22]

When gout is suspected, suggested laboratory investigation includes sUA, comprehensive metabolic panel (for blood sugar, kidney function, and liver function), and lipid panel. Since diabetes and metabolic syndrome are highly comorbid with gout, the glycated hemoglobin A1c may also be measured. The presence of cardiovascular and other associated comorbidities should also be assessed.[20]

TREATMENT

The treatment of patients with gout involves 2 key objectives: (1) rapid and complete relief of symptoms during an acute gout flare; and (2) elimination of uric acid deposits by completely dissolving existing MSU crystals. This ultimately should lead to complete absence of further gout flares.[23] While lifestyle factors such as consumption of red meat, seafood, food and drink rich in fructose, and moderate to heavy intake of beer and hard liquor raise sUA levels and increase the risk of an acute gout flare, there is no evidence to support the premise that lifestyle modification improves outcomes in patients with gout. Nonetheless, evidence suggests that diet and physical activity can lower sUA levels 10% to 18%.[20,24] Therefore, a healthy lifestyle is recommended and consumption of beer and spirits discouraged.[20,24] Hydration is important and patients should be encouraged to drink at least 2 liters of water daily.[24,25]

Acute gout flare

The rapid onset of severe pain during an acute gout flare leads to impairment of patient function, emphasizing the importance of providing rapid pain relief with appropriate abortive medication. Lowering the sUA level is never a goal of treatment during an acute flare, as any alteration of sUA during a flare, whether up or down, will worsen and/or prolong the flare. The rapid onset of pain and need for rapid introduction of abortive medication underscores the importance of providing patients with a treatment plan for managing an acute gout flare wherever they may be. Patients should have readily available 1 or more of the 3 abortive medications—colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or glucocorticosteroids—and advised to have the medication on hand to use immediately upon the onset of a flare.

Colchicine, NSAIDs, and glucocorticosteroids are all effective for the management of an acute gout flare and are recommended, but insufficient head-to-head comparisons prevent a recommended hierarchy of use.[26] The choice of medication for an acute gout flare should be individualized based on patient characteristics (comorbidities) and medication safety.[20,26] The use of 2 medications in combination is recommended for flares that are severe, hard to treat, or lengthy.[26]

Colchicine has been used for centuries for an acute gout flare, with doses traditionally administered until occurrence of unacceptable gastrointestinal (GI) side effects. This approach is no longer recommended as a recent study found that administration of colchicine 1.2 mg at the onset of pain followed by 0.6 mg in 1 hour (total of 1.8 mg) is as effective with a lower incidence of adverse GI events.[27]

Among the NSAIDs, indomethacin, naproxen, and sulindac are approved by the FDA for an acute gout flare, although other NSAIDs have similar effectiveness when used in high doses for 1 to 2 weeks.[23,25,26] In addition to upper GI bleeding, NSAIDs are associated with major adverse cardiovascular events, particularly myocardial infarction and coronary heart disease death; both of these adverse events carry black box warnings for all NSAIDs for any use. These

cardiovascular risks appear greatest with COX-2-specific inhibitors, as well as diclofenac and possibly ibuprofen, over at least 4 weeks of use. All NSAIDs doubled the risk of heart failure causing hospitalization.[28] Finally, NSAIDs are to be avoided in patients with chronic kidney disease of all stages.

Corticosteroids are rapidly effective when given via the oral, intramuscular, or intra-articular route of administration. Oral prednisone 20 to 40 mg is administered once daily until symptoms improve and tapered over 10 to 14 days. Methylprednisolone "dosepack" given over 6 days is not recommended as it is not long enough in duration, and patients often have a rebound flare after the course of medication is complete.[29] If oral administration is not appropriate, intramuscular administration of a long-acting corticosteroid is an option. Intra-articular administration may be most useful in patients with a severe monoarticular flare in whom colchicine or an NSAID is contraindicated.[23] Risk of adverse events from oral or intramuscular steroids, eg, fluid retention, psychiatric symptoms, GI upset, and worsening of patient comorbidities (especially diabetes) are important considerations as well.

Chronic gout

As gout is a disease of chronic crystal deposition, patients with prior gout flares and current hyperuricemia should be considered candidates for urate-lowering therapy (ULT) in order to prevent future flares and to minimize or possibly reverse joint, bone, and soft tissue damage.[24] ULT is also indicated for patients with tophaceous gout and gout with uric acid nephrolithiasis or renal function impairment.[23,24] ULT should not be initiated until a gout flare has completely subsided to avoid perpetuating the flare.[30]

A treat-to-target approach should be utilized wherein ULT is initiated and intensified as needed to achieve and maintain the target sUA level <6.0 mg/dL.[20] In patients with tophi, an sUA ≤5 mg/dL is recommended to increase the speed of tophi reduction.[20] Initiation of ULT is associated with gout flares for the first 6 months or so of treatment, thus prophylactic use of anti-inflammatory therapy (eg, colchicine) is recommended during that time frame.[26]

Several options for lowering sUA are available, including xanthine oxidase inhibitors (allopurinol, febuxostat) that prevent the production of uric acid, uricosuric agents (probenecid), and one biologic agent (pegloticase) that enzymatically degrades uric acid to allantoin.[20,24] Among these, a xanthine oxidase inhibitor is recommended as first-line therapy and allopurinol is the most commonly used because of its low cost and extensive clinical use, but also because of its relatively good safety and efficacy.[20] Initiating therapy with a low dose (100 mg/day) and gradually increasing by 100 mg every 1 to 2 weeks until an sUA ≤6 mg/dL is achieved can minimize the risk of a hypersensitivity reaction, including exfoliative, urticarial, and purpuric lesions, and Stevens-Johnson syndrome, as well as an acute gout flare.[20] The dose of allopurinol needs to be reduced in patients with decreased renal function who are concurrently taking a thiazide as hypersensitivity reactions are more likely.[31] A daily dose greater than 300 mg is often needed to achieve the target sUA level, particularly in those with moderately severe tophaceous gout.[32] The maximum recommended dose is 800 mg/day, with doses above 300 mg given as a divided daily dose primarily to avoid GI side effects.

Febuxostat is another xanthine oxidase inhibitor that may be used in those who are intolerant of or do not respond to adequate doses of allopurinol. Febuxostat is approved by the FDA at a daily dose of 40 mg or 80 mg, but American College of Rheumatology guidelines suggest usage up to 120 mg.[24] It is at least as effective as allopurinol in reducing sUA, and in some studies has shown to be more effective.[33] In addition to liver function abnormalities, febuxostat may be associated with a slightly higher incidence of cardiovascular thromboembolic events.[34]

Pegloticase is an injectable recombinant uricase that catalyzes the oxidation of uric acid to the inert, water-soluble metabolite allantoin. It needs to be administered under careful supervision in an infusion center, as serious allergic reactions, even anaphylaxis, are common. Pegloticase should not be combined with other ULT medications. In allopurinol-refractory patients, combined analysis of 2 randomized, placebo-controlled studies showed that 42% of those treated with pegloticase 8 mg biweekly achieved an sUA <6.0 mg/dL at 6 months.[35] Patients reported significant and clinically meaningful improvements in global disease activity, pain, physical function, and health-related quality of life.[36]

When xanthine oxidase inhibitors fail to achieve the target sUA or cannot be used, uricosuric medications can be considered. The only one presently approved by the FDA is probenecid, which is dosed at 500 mg a day and gradually increased to a maximum of 2500 mg a day as needed. It is not to be used when patients have creatinine levels <50 mg/dL or uric acid urolithiasis.

Several medications that lower sUA are in clinical development. Lesinurad, a uricosuric medication that is a selective uric acid reabsorption inhibitor in the kidney, is under review by the FDA. In patients not achieving their target sUA of <6.0 mg/dL with allopurinol monotherapy, the addition of lesinurad 200 mg or 400 mg led to a significantly higher proportion of patients reaching this sUA goal at 6 months when compared with allopurinol alone (P<.0001).[37] The incidence of renal adverse events with lesinurad 200 mg plus

TABLE Care plan for a patient with gout[43]

	Acute intermittent gout	Chronic gout
Goals	To recognize and manage acute flare To treat pain as quickly as possible	To prevent future flares To slow and reverse joint and soft tissue damage
Educational points	Promote patient self-management for very early recognition and treatment of acute flare symptoms Provide an action plan and a means to record flare number, duration, and intensity as well as medication for treating acute flares at home Provide guidance on when to call the clinic during a flare and what to do if acute treatment is not effective Provide guidance on the most likely adverse drug reactions	Discuss the silent phases of the disease (between flares) and the importance of monitoring sUA levels and continued adherence with ULT Inform patients that initiation of ULT may increase the early risk for acute flare, and provide flare prophylaxis for at least 6 months Remind patients that acute flares during treatment should be treated with anti-inflammatory medications but to continue ULT for long-term flare prevention Provide guidance on lifestyle modifications to reduce sUA levels Provide guidance on the most likely adverse drug reactions

Abbreviations: sUA, serum uric acid; ULT, urate-lowering therapy.

allopurinol was comparable to placebo plus allopurinol, but was more frequent with lesinurad 400 mg plus allopurinol. Predominantly, reversible doubling of the serum creatinine was more frequent in both lesinurad groups compared with placebo. Lesinurad has also been investigated in combination with febuxostat. Compared to febuxostat alone, the addition of lesinurad 400 mg led to a significantly higher proportion of patients reducing their sUA to <5 mg/dL at 6 months.[38]

Flare prophylaxis

The mobilization of uric acid from tissues that occurs with the initiation of ULT often results in an acute gout flare (also known as a mobilization flare). To forestall patient concerns and foster adherence to ULT, 3 actions are suggested. First, patients should be educated about this possibility, that it is generally intermittent and temporary, and resolves over weeks to months as uric acid stores eventually become depleted. Second, it is advised to "start low and go slow" when initiating ULT such as allopurinol (febuxostat has only one dosage recommendation: start at 40 mg and increase to 80 mg after 2 weeks if not at target).[20] Third, prophylactic therapy with colchicine 0.6 mg once or twice daily can be initiated 1 to 2 weeks prior to initiating ULT as this may prevent up to 80% of flares over 3 to 6 months.[39-41] Diarrhea may be more frequent than with placebo, but adverse events with colchicine are otherwise similar to those occurring in patients treated with placebo.[42] Although NSAIDs in low doses and steroids in low doses can also be used for flare prophylaxis, evidence to support their use is lacking, and long-term use of these medications must be done cautiously.[20] Although 6 months is suggested, the duration of prophylactic therapy is unclear and should be determined based on a patient's flare frequency, gout duration, and the presence and size of tophi.[20]

PATIENT MONITORING AND EDUCATION

The success of ULT has typically focused on the sUA level as this is a surrogate marker of disease activity. Monitoring should also include the frequency of acute gout flares and tophi size. When patients are at the sUA goal using ULT, guidelines suggest testing the sUA, along with liver function tests, and kidney function every 6 months.

The chronic nature of gout and the need for long-term ULT in the majority of patients make it clear that patient education is an important component of management. Patients should be educated about the consequences of gout, its association with other chronic diseases, and the importance of their concomitant management. The importance of notifying providers about changes in prescribed and over-the-counter medications should be reinforced. Patients should be educated about the dual mechanism nature of gout and the limited role of diet modification, the need for and roles of medications for acute and chronic management, and the importance of adherence, particularly with ULT. Patients should be made aware that acute gout will occur, but that treatment will be modified to reduce its occurrence and severity. It is especially important to develop a written plan with the patient to guide the self-management of an acute gout flare at home, if possible **(TABLE)**.[43] Patients should also be encouraged to keep a log of the occurrence and severity of an acute gout flare and how the flares were managed.

SUMMARY

Gout is a chronic inflammatory condition that is increasing in prevalence and commonly associated with other chronic diseases such as obesity, diabetes mellitus, hypertension, hypercholesterolemia, chronic kidney disease, cardiovascular disease, and thromboembolic disorders.[2] These associations make the management of patients with gout more complex. Although identification of MSU crystals in synovial fluid is diagnostic, a presumptive diagnosis of gout can be made clinically based on the presence of hyperuricemia, rapid development of pain, tenderness, and swelling in a single toe (male) or elbow or finger joint (female), and family history.

Gout is increasingly recognized as a heterogeneous disease requiring individualized treatment. A healthy lifestyle is always recommended and patient education is critical to support self-management and long-term adherence. Anti-inflammatory therapy, typically colchicine or an NSAID, is recommended for management of an acute gout flare, while ULT may be used in patients with frequent or severe acute gout, tophi, urolithiasis, renal function impairment, or other complications of gout. Allopurinol is first-line ULT for most patients, although febuxostat and probenecid are effective options and pegloticase is useful in selected patients. New medications, such as lesinurad, are on the horizon. ●

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Pharmacologic Approach to Obesity Management

Robert F. Kushner, MD, MS, FACP

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading this article on obesity management, the family physician will be able to:

1. Identify patients who are candidates for pharmacotherapy to promote weight loss
2. List the short- and long-term goals of pharmacotherapy
3. Initiate pharmacotherapy in consideration of medication and patient factors
4. Implement strategies to discuss weight-loss medications with patients

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and competency regarding primary care management of obesity.

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SPONSORSHIP

This activity is sponsored by the IAFP/Family Practice Education Network and Primary Care Education Consortium.

SUPPORTER

This activity is supported by educational grants from Novo Nordisk, Inc. and Takeda Pharmaceuticals U.S.A., Inc.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Illinois Academy of Family Physicians/Family Practice Education Network and PCEC. The Illinois Academy of Family Physicians/Family Practice Education Network is accredited by the ACCME to provide continuing medical education for physicians.

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Release Date: 10 Dec 2015
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CASE STUDY #1. JW is a 58-year-old man with a body mass index (BMI) of 38 kg/m^2 (height, 177.8 cm; weight, 120 kg) who has lost 3.6 kg (3% body weight) since initiating lifestyle interventions 6 months ago. He is an information technology executive who travels extensively for work. He was referred to a registered dietitian who helped him develop strategies to reduce his portion sizes and make healthier choices at restaurants. When traveling, he has also been going to fitness centers at hotels a few times a week. JW takes esomeprazole 40 mg once daily for gastroesophageal reflux disease and occasionally takes sildenafil for erectile dysfunction. JW is eager to lose more weight, but he finds it difficult to make further lifestyle modifications.

CASE STUDY #2. DS is a 61-year-old retiree who had a BMI of 38.5 kg/m^2 (height: 166 cm; weight, 106 kg) when she was diagnosed with type 2 diabetes mellitus (T2DM) at which time she decided it was time to lose weight. Since joining Weight Watchers and starting a neighborhood walking group, DS lost 5.1 kg (4.8% of her initial body weight). After an additional 6 months of intensified lifestyle management that included monthly sessions with a registered dietitian and working with a personal trainer at her local YMCA, DS lost another 1.2 kg (1.1% of initial body weight). However, over the next 7 months, DS found it difficult to maintain her intensive lifestyle changes and regained 1.9 kg. Her primary care physician (PCP) subsequently prescribed orlistat 120 mg 3 times a day, which she took for 3 months, helping her to lose 1.6 kg. However, she experienced frequent defecation (sometimes with urgency). Her glycated hemoglobin A1c (HbA1c) was 9.2% at baseline (when she first implemented lifestyle interventions for weight loss) and has ranged from 7.2% to 7.8% during the past 14 months. Her HbA1c is currently 7.4% and she is taking saxagliptin and metformin extended-release (ER) 5/1000 mg once daily. DS also has hypertension; her blood pressure is 134/82 mm Hg on enalapril and hydrochlorothiazide (10/25 mg once daily). Her current weight is 100 kg.

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ACKNOWLEDGMENT
Editorial support was provided by Dana Randall, MS, PharmD, RPh; Gregory Scott, PharmD, RPh.

SUPPORT
This CME article is jointly sponsored by the Illinois Academy of Family Physicians/Family Practice Education Network and Primary Care Education Consortium and supported by educational grants from Novo Nordisk, Inc. and Takeda Pharmaceuticals U.S.A., Inc.

TREATMENT OF OBESITY

Obesity (BMI ≥30 kg/m^2) is a chronic disease requiring a range of lifestyle and medical interventions.[1] A suggested approach to managing patients with overweight or obesity in the primary care setting was developed by the American Heart Association, American College of Cardiology, and The Obesity Society (AHA/ACC/TOS) in 2013.[2] In 2015, the Endocrine Society published guidelines for the pharmacologic management of obesity.[3] For patients with obesity, the initial weight loss goal is 5% to 10% of baseline body weight within 6 months as this has been shown to yield significant health benefits.[2] The Look AHEAD (Action for Health in Diabetes) trial (N=5145) revealed numerous benefits associated with lifestyle interventions that resulted in modest weight loss (8.6% at 1 year), including enhanced glycemic control, improved lipid profile, and a reduced requirement for medications for diabetes, hypertension, and dyslipidemia.[4] In addition, at 1 year, lifestyle interventions were associated with improved symptoms of depression, obstructive sleep apnea, and sexual dysfunction and fewer patients developed symptoms of urinary incontinence.[5-8] Long-term goals are to achieve further weight loss, if appropriate, or to maintain weight loss.

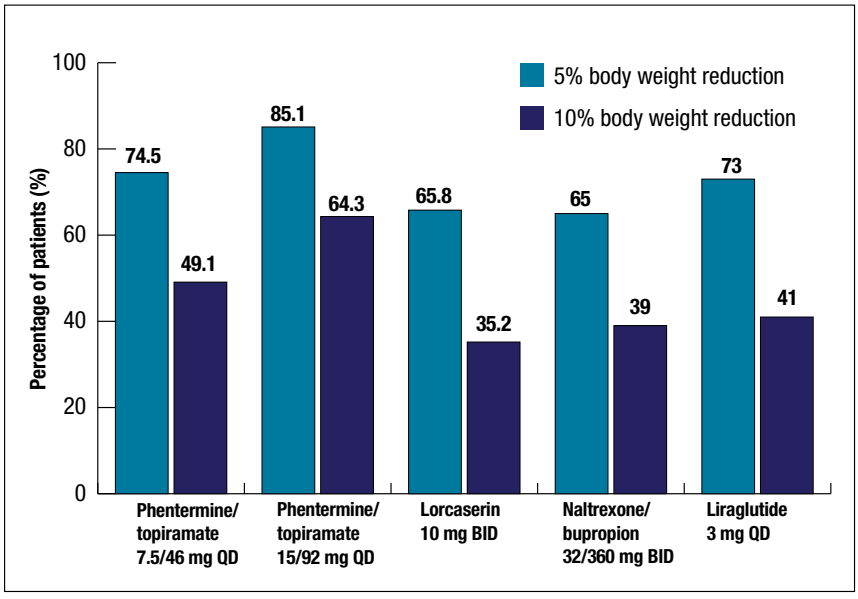
Patient-centric approach to weight management

As in the 2 case studies, patients with obesity have likely faced numerous challenges related to their weight and have tried to lose weight multiple times.[2] But achieving and maintaining modest weight loss is difficult. In a population-based cohort study from the United Kingdom, the annual probability of attaining normal weight (BMI 18.5-24.9 kg/m^2) was 1 in 210 for men and 1 in 124 for women with obesity (BMI 30.0–34.9 kg/m^2).[9] Talking with patients about their weight loss-related experience and factors motivating them for further weight loss efforts is, therefore, particularly important. This will help the provider and patient determine the appropriateness of weight loss, the patient's readiness for change, and treatment goals. This process can be facilitated using motivational interviewing, such as asking the patient, "How prepared are you to make changes to your diet, to be more physically active, and to use behavior strategies such as recording your weight and food intake?"[2]

Body weight is a sensitive issue for most patients, partly because they have likely encountered weight bias in their daily lives as well as from health care providers. Interestingly, weight discrimination may increase the risk for obesity.[10,11] It is, therefore, important to interact with the patient respectfully and use appropriate language. Words such as body mass index, unhealthy weight, and excess weight are preferred by patients over words such as heaviness,

obesity, or excess fat.[12,13] The 5 A's of obesity counseling (assess, advise, agree, assist, arrange) provide a framework for the clinician to engage a patient in a conversation about weight.[14] Following this framework can help the clinician provide advice and support to a patient. By learning about patients' experiences and listening to their concerns and motivation, the clinician can offer encouragement and discuss potential treatment options.

FIGURE Percentage of patients who achieved 5% and 10% body weight reduction after 1 year of treatment with medication in combination with lifestyle intervention[21-24]



Abbreviations: BID, twice daily; QD, once daily.

Patients were treatment completers in clinical trials.

Pharmacologic therapy for obesity

Lifestyle management and behavior modification are cornerstones of management for people with obesity, but often do not result in achieving and maintaining the targeted weight loss and improvement in associated comorbid conditions. Consequently, pharmacotherapy is needed as adjunctive therapy for many people with obesity, including those with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 with at least 1 obesity-associated comorbidity such as T2DM, hypertension, or dyslipidemia.[2]

Weight-loss medication is useful to suppress the appetite and/or improve satiety, reduce calorie ingestion, and produce the 500 to 750 kcal/day negative energy balance required for weight loss.[2] Pharmacotherapy prescribed alone is not as effective as pharmacotherapy prescribed as part of a comprehensive weight management program.[15] Also, in placebo-controlled clinical trials of approved weight loss medications, significantly more patients receiving medication versus placebo in addition to lifestyle interventions achieved 5% to 10% loss of body weight.[16-20]

When considering whether weight loss medication is appropriate for a patient who is overweight or obese, the clinician needs to consider a number of factors such as whether the patient is motivated to lose weight and will engage in healthy lifestyle behaviors. Since many patients are apprehensive to use medications based on past experiences or misunderstandings, it is important to have a brief discussion of how they work and what to expect. It is important to emphasize that the purpose of medication is to help patients adhere to a lower calorie diet more consistently in order to achieve more sufficient weight loss and health improvements when combined with increased physical activity.[2] The clinician and the patient should also discuss and weigh the potential risks of a medication against the potential benefits of successful weight loss.

Medications for short-term use

Central noradrenergic agents (phentermine, diethylpropion, phendimetrazine, and benzphetamine) have been available since the 1950s. However, these appetite suppressants have not been evaluated in randomized controlled trials for chronic weight management and are approved for only short-term (<12 weeks) use. They should be used with caution and close monitoring if prescribed beyond 12 weeks.

Medications for long-term use

Medications approved for long-term weight management are: orlistat (Xenical, Alli), lorcaserin (Belviq), phentermine/topiramate ER (Qsymia), naltrexone/bupropion ER (Contrave), and liraglutide (Saxenda). All agents approved for long-term weight management appear to be nearly similarly effective at 1 year, although results may be dose-dependent (**FIGURE**). In randomized controlled trials, approximately 65% to 75% of patients who completed treatment lost ≥5% of initial body weight and 35% to 50% of patients lost ≥10% body weight.[21-24] The highest dose of phentermine/topiramate ER (15/92 mg) was associated with a slightly greater response; however, response associated with the lower dose of phentermine/topiramate (7.5/46 mg) was similar to that of other agents. Given comparable response to weight-loss agents during long-term use, drug selection for patients

who are candidates for drug therapy primarily depends on individual patient factors, medication tolerability, and cost/availability. The mechanisms of action, dosage regimens, contraindications, and considerations for use for available long-term weight-loss medications are summarized in the **TABLE**.

All weight-loss medications are contraindicated in pregnancy. The centrally acting agents are either contraindicated (phentermine/topiramate ER and naltrexone/bupropion ER) during or within 14 days of monoamine oxidase inhibitor use or require caution because of the risk for serotonin syndrome (lorcaserin). Patients should be monitored for thoughts of suicide or new or worsening depression when taking the centrally acting agents or liraglutide. Disturbances in attention and memory are precautions for lorcaserin and phentermine/topiramate ER use, and both are Schedule IV medications.

Orlistat

Of the agents approved for long-term use, orlistat, a pancreatic lipase inhibitor, is the only peripherally acting agent and is available over the counter and by prescription.[25] A meta-analysis of patients with obesity who received orlistat 120 mg or placebo 3 times daily revealed significant differences in the incidence of gastrointestinal adverse events between groups.[25] Gastrointestinal adverse events, including oily spotting, flatulence, and fecal urgency, are generally mild and occur within the first 12 weeks of orlistat therapy; however, these symptoms may be a significant barrier to patient acceptance.[25] Fewer than 10% of patients with obesity prescribed orlistat take the medication for at least 1 year.[26] Orlistat has been associated with the development of kidney stones in patients at risk for renal insufficiency and rare cases of serious liver injury.[27]

Lorcaserin

Lorcaserin is a selective 5-HT2C serotonin agonist with little affinity for other serotonergic receptors such as 5-HT2B.[17] Fenfluramine was a 5-HT2B receptor agonist withdrawn from the market in 1997 due to valvulopathy. Despite these differences in binding, patients treated with lorcaserin should be monitored for valvular heart disease.[28] Headache and dizziness may be the most bothersome adverse effects to patients as these were the most common adverse events associated with discontinuation in one multicenter study.[17] Lorcaserin may interact with other serotonergic drugs (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, triptans, bupropion, dextromethor-phan, and St. John's wort), increasing the risk of serotonin syndrome.[29] Clinicians should, therefore, use caution when prescribing lorcaserin to patients with comorbid depression or migraines who are also taking a serotonergic agent. The 10 mg twice-daily dose of lorcaserin should not be increased.[29]

Phentermine/topiramate ER

Phentermine/topiramate ER is a combination medication that blunts appetite (phentermine) and prolongs satiety (topiramate).[30] To minimize adverse events, the combination medication includes a low dose of each medication. Phentermine/topiramate ER provides multiple dosing options to tailor therapy. Women of childbearing potential should use effective means of birth control and complete a pregnancy test before initiation of therapy and monthly thereafter, as topiramate is teratogenic (orofacial clefts).[31,32] In addition to causing paresthesia and taste alterations, carbonic anhydrase inhibition by topiramate may also decrease concentrations of sodium bicarbonate and potassium and increase the risk of oxalate nephrolithiasis.[18] Phentermine/topiramate ER is associated with a dose-related increase in the incidence of depression- and anxiety-related events and cognitive impairment.[18]

Naltrexone/bupropion ER

Naltrexone/bupropion ER is another centrally acting agent with a dual mechanism of action. Combined, naltrexone, an opioid antagonist, and bupropion, a weak dopamine and norepinephrine uptake inhibitor, increase the firing rate of pro-opiomelanocortin (POMC) neurons in the hypothalamus (appetite regulatory center) and reduce food intake via effects on the mesolimbic dopamine circuit (reward system).[33] The combined use of naltrexone and bupropion is thought to overcome the compensatory mechanisms that limit the efficacy of either agent used alone.[33] Naltrexone/bupropion ER provides an option for patients who report food cravings as a barrier to dietary changes.[19] Nausea was the most commonly reported adverse event in a 56-week clinical trial and was the most common reason for treatment discontinuation; however, most participants who reported nausea did not discontinue treatment.[19] In order to reduce nausea, a weekly dose escalation schedule is used over the first month of treatment. Because of the bupropion component, this combination agent should not be used in patients with seizure disorders or in patients with a current or prior diagnosis of anorexia or bulimia nervosa.[34] Due to the naltrexone component, the drug cannot be used in patients who require opioid treatment for pain control.

Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist previously approved for the treatment of patients with T2DM.[20] Liraglutide also promotes satiety and reduces caloric intake.[35] Liraglutide is associated with dose-

TABLE **Weight-loss medications approved for long-term use in the United States**

Generic (brand) name Dosage forms Mechanism of action US FDA approval for weight loss[a] Drug schedule	Dosage regimen(s)	Considerations[b]	Most common adverse events in clinical trials	Responsiveness criteria
Orlistat (Alli, Xenical) • 60 mg, 120 mg capsules • Pancreatic lipase inhibitor • 1999 • Unscheduled	• OTC: 60 mg TID with meals • Prescription: 120 mg TID with meals	• GI events may increase with high-fat diet • Patients should take a multivitamin with fat-soluble vitamins • Hepatotoxicity • Oxalate kidney stones • Monitor cyclosporine, levothyroxine, warfarin, and antiepileptic drug levels	• Oily spotting, 27% • Flatus with discharge, 24% • Fecal urgency, 22% • Fatty/oily stool, 20% • Oily evacuation, 12% • Increased defecation, 11% • Fecal incontinence, 8%	—
Lorcaserin (Belviq) • 10 mg tablets • 5-HT2C serotonin agonist • 2012 • Schedule IV	10 mg BID	• Serotonin syndrome (SSRIs, SNRIs, MAOIs, triptans, bupropion, dextromethorphan, St. John's wort) • Valvular heart disease • Monitor depression, suicidal thoughts • Disturbances in attention/memory • Priapism	• Headache, 17% • Dizziness, 9% • Nausea, 8% • Fatigue, 7%	If <5% weight loss at 12 wk, discontinue
Phentermine/topiramate ER (Qsymia) • 3.75/23, 7.5/46, 11.25/69, and 15/92 mg capsules • Phentermine: sympathomimetic • Topiramate: GABA receptor modulation, glutamate antagonism, carbonic anhydrase inhibitor • 2012 • Schedule IV	• Initial dose: 3.75/23 mg once daily in the morning for 14 days • Maintenance dose: 7.5/46 mg • Maximum maintenance dose: 15/92 mg	• Monthly pregnancy test required • Monitor depression, suicidal thoughts, heart rate • Mood and sleep disorders • Disturbances in attention/memory • Metabolic acidosis • Kidney stones • Discontinue gradually	• Constipation, 15% • Paresthesia, 14% • Dry mouth, 14% • Dysgeusia, 7% • Dizziness, 7%	If <3% weight loss at 12 wk on 7.5/46 mg, can increase to 15/92 mg. If <5% weight loss after 12 wk on 15/92 mg, discontinue
Naltrexone/bupropion ER (Contrave) • 8/90 mg tablets • Naltrexone: opioid receptor antagonist • Bupropion: dopamine/norepinephrine reuptake inhibitor • 2014 • Unscheduled	• Week 1/Initial dose: 1 tablet AM • Week 2: 1 tablet AM and PM • Week 3: 2 tablets AM, 1 tablet PM • Week 4/ Maintenance dose: 2 tablets BID	• Monitor depression, suicidal thoughts, heart rate, blood pressure • Glaucoma • Hepatotoxicity • Bupropion is a CYP2D6 inhibitor • Reduce dose with concomitant CYP2B6 inhibitors and avoid with CYP2B6 inducers	• Nausea, 33% • Constipation, 19% • Headache, 18% • Vomiting, 11% • Dizziness, 10% • Insomnia, 9%	If <5% weight loss after 12 wk of maintenance dose, discontinue
Liraglutide (Saxenda) • 0.6, 1.2, 1.8, 2.4, and 3 mg solution for subcutaneous injection in prefilled, multidose pens • GLP-1 receptor agonist • 2014 • Unscheduled	• Initial dose: 0.6 mg/day • Dose increase: 0.6 mg weekly • Maintenance dose: 3 mg/day • Note: Dose can be injected any time of day	• Acute pancreatitis • Acute gallbladder disease • Renal impairment • Monitor depression, suicidal thoughts, and heart rate • Delays gastric emptying and may impact absorption of concomitantly administered medications	• Nausea, 39% • Hypoglycemia (T2DM), 23% • Diarrhea, 21% • Constipation, 19% • Vomiting, 16% • Dyspepsia, 10% • Eructation, 5%	If <4% weight loss after 16 wk treatment, discontinue

[a]All medications are indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index of ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of ≥1 weight-related comorbidity such as type 2 diabetes mellitus, hypertension, or dyslipidemia.

[b]Does not include contraindications or warnings; see prescribing information.

Abbreviations: BID, twice daily; GABA, gamma-aminobutyric acid; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; MAOI, monoamine oxidase inhibitor; OTC, over the counter; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; TID, 3 times daily; T2DM, type 2 diabetes mellitus; wk, weeks.

Source: US Food and Drug Administration. Drugs@FDA. wwwaccessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

dependent weight loss in doses up to 3.0 mg/day.[20] Gastrointestinal adverse effects were the most common cause of discontinuation in a 56-week liraglutide clinical trial. Most reports of nausea and vomiting occurred during the first 4 to 8 weeks of liraglutide treatment and coincided with dose escalation. To reduce the incidence and severity of nausea, it is recommended that the dose of liraglutide be initiated at 0.6 mg once daily and increased by 0.6 mg weekly to the recommended dose of 3 mg once daily. Clinicians should be aware that liraglutide delays gastric emptying and may impact the absorption of concomitantly administered oral medications.[36] Use of liraglutide may be limited by patient acceptability of an injectable medication as well as by its relative high cost.

CASE STUDIES (continued)

Initiating pharmacologic therapy for weight loss should follow a patient-centric approach to individualize therapy based on patient and medication factors. Patient education and support are critical and may be best provided through involvement of other members of the health care team, particularly to provide ongoing lifestyle management and behavior modification support.

CASE STUDY #1. After discussion of the medication options, phentermine 3.75 mg/topiramate 23 mg ER was prescribed for 2 weeks, followed by a dose escalation to phentermine 7.5 mg/topiramate 46 mg ER weekly. JW has now returned to his PCP for his 3-month follow-up visit. He has lost 3.5 kg (3% of body weight) and has not experienced any bothersome effects from the medication. JW and the PCP discuss JW's long-term weight-loss goals and the steps JW would like to take to achieve them. The PCP continues the medication at the same dose and encourages JW to continue to limit his portion sizes at every meal and try to increase the number of days that he exercises.

CASE STUDY #2. DS was prescribed liraglutide 3 mg once daily (initial dose, 0.6 mg once daily) 3 months ago; saxagliptin was discontinued and metformin continued. Since starting liraglutide, DS has lost 6.8 kg (6.8% of her body weight since initiation of liraglutide). DS reported feeling nauseous for the first few weeks after starting liraglutide but no longer. Her daily log shows that she has experienced 2 episodes of mild hypoglycemia; she has not had any hypotensive episodes. Her current blood pressure is 130/80 mm Hg and her HbA1c is 7%. The PCP encourages DS to continue the healthy habits she has developed (including recording her blood pressure and blood glucose levels) and reminds her that her blood pressure and blood glucose may come down further. The PCP also suggests that DS follow up with her registered dietitian to develop a strategy should DS encounter a weight loss plateau.

Monitoring use of medications for long-term use

Treatment should be reassessed 3 to 4 months after initiating pharmacologic therapy to determine if an adequate response has been achieved (**TABLE**). If the responsiveness criterion for a given medication is not met, the medication should be discontinued and an alternate weight-loss medication initiated, as appropriate for an individual patient. Phentermine/topiramate is unique since a higher dose can be prescribed if the patient did not achieve the responsive weight loss threshold. None of the drugs approved for long-term use have been investigated in combination with other weight-loss agents. In patients with T2DM, blood glucose should be monitored as weight loss may increase the risk of hypoglycemia, particularly in those treated with insulin or insulin secretagogues. Also, dose adjustment or discontinuation of antihypertensive agents may be required if weight loss is associated with reduced blood pressure. There are no data available regarding whether any of the medications approved for chronic weight management reduce the risk of heart attack, stroke, or death.

CONCLUSION

The availability of 5 medications with varying pharmacology approved for long-term use provides clinicians with a variety of treatment options for weight management. Weight-loss medications should be prescribed in conjunction with comprehensive lifestyle management and considered for patients who have been unable to achieve or maintain a healthier body weight. Differences among the long-term medications enable treatment to be individualized. Treatment response should be assessed 3 to 4 months after initiating a long-term weight-loss medication, with modification made, if necessary, based on amount of weight lost and patient tolerability. ●

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Ambulatory Glucose Profiling

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INTRODUCTION

This article introduces ambulatory glucose profiling, an evolving approach to monitoring blood glucose. The concept of ambulatory monitoring of glucose data is analogous to ambulatory monitoring of heart rate and rhythm using Holter monitoring or ambulatory monitoring of blood pressure to determine when and what changes to prescribed therapy are necessary. A benefit of ambulatory glucose profiling is that it aggregates large amounts of glucose monitoring data so that variations in blood glucose can be easily identified. The scope of this article is limited and does not include discussion of how integrating ambulatory glucose profiling can be integrated into clinical practice.

Current measures of blood glucose

Diabetes management is essentially a balancing act between maintenance of good glycemic control to reduce the risk of complications, particularly end organ damage and avoidance of severe hypoglycemia.[1] In most patients with diabetes mellitus, however, glycemic control remains suboptimal despite pharmacological advances and technological advances in insulin delivery devices and glucose monitoring.[2,3] A major factor in poor glycemic control is lack of adherence to prescribed therapeutic agents, most especially insulin, due in part to fear of hypoglycemia.[2,4-6]

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DISCLOSURES

Dr. Wright discloses that he is on the advisory board and speakers' bureaus for Abbott Diabetes Care Inc.; Boehringer Ingelheim GmbH; and Eli Lilly and Company. He is on the advisory board for AstraZeneca and Voluntis and does contracted research for Abbott Diabetes Care Inc.

Dr. Manivannan discloses that she has no real or apparent conflicts of interest to report.

ACKNOWLEDGMENT

Editorial support was provided by Angela Cimmino, PharmD; Gregory Scott, PharmD, RPh. The authors thank Roger Mazze, PhD, for his helpful suggestions in the development of this article.

SUPPORT

This article is sponsored and developed by Primary Care Education Consortium.

To further complicate matters, there is growing evidence that glycemic variability—fluctuations in the blood glucose level—may contribute to the development and progression of micro- and macrovascular disease in individuals with diabetes, including an association with increased carotid intima media thickening.[7,8] In the Diabetes Control and Complications Trial, risk of retinopathy progression was significantly greater among conventionally treated vs intensively treated patients, despite comparable glycated hemoglobin A1c (HbA1c) —a finding potentially due to the greater frequency and magnitude of glycemic excursions in conventionally treated patients.[9] It is thought that glycemic variability causes an overproduction of potentially harmful reactive oxygen species and increased oxidative stress resulting in worsened endothelial function and damaged mitochondria and genomic DNA.[10,11] Evidence also indicates that glycemic variability is a strong predictor of hypoglycemia, correlates with poor glycemic control, and is predictive of patient satisfaction with an intensive insulin regimen.[2,12,13] These observations make a compelling argument for glycemic variability as an important measure of glycemic control, and its minimization as an important treatment goal.

HbA1c is considered the gold standard indicator of glycemic control in diabetes management due to its demonstrated correlation with the incidence of micro- and macrovascular complications.[14] However, HbA1c reflects mean blood glucose over 8 to 12 weeks, and cannot characterize diurnal glucose patterns which are essential for safe and effective adjustment of glucose-lowering therapy and the avoidance of glucose variability—most notably, extremes of hypo- and hyperglycemia.[14,15] For decades, self-monitoring of blood glucose (SMBG) has been the standard measure of glycemic control to guide day-to-day adjustment of therapy. Limitations of SMBG include underreporting (omission of undesirable values), over-reporting (addition of values within target), imprecise reporting, lack of overnight glucose readings, and its episodic nature, all of which result in missed significant hypo- and hyperglycemic events.[1]

The advent of continuous glucose monitoring (CGM) allows for the collection of continuous glucose data via a sensor (<5 mm in diameter) placed beneath the skin on the abdomen or arm that takes a reading at set intervals (eg, every 1 to 5 minutes) and can be used for 3 to 7 days at a time.[16] CGM can provide real-time feedback on current glucose levels as well as

retrospective data that provides a more accurate view of glucose patterns over a given time period compared with SMBG.[1] A number of studies, including 2 meta-analyses, have demonstrated the efficacy of CGM in improving glycemic control (including reduced HbA1c) and reducing hypoglycemia.[17-20]

Despite its benefits, CGM is currently used in diabetes management in only a small percentage of patients with type 1 diabetes (3% among young patients with T1D [≤25 years old], and 14% among 26 to 49 year old patients with T1D) and a negligible number with type 2 diabetes.[3] While underutilization may be partially attributed to limited reimbursement and patients' perceptions regarding the complexity and inconvenience of CGM, barriers to clinicians' incorporating CGM into their practice are another key factor.[16] Chief among these is the daunting time investment required to become proficient at managing and interpreting the CGM data.[16] There are currently 3 commercial CGM device manufacturers, each requiring its own proprietary software to download and analyze CGM data and create reports, with a myriad of reporting options and no standardization among them regarding report output.[16]

Ambulatory glucose profiling

Given the demonstrated benefits of CGM, there is a need for standardization of blood glucose data analysis and presentation in a straightforward and intuitive manner in order to convert the data derived from CGM into actionable information.[2,14] This process can be accomplished with the ambulatory glucose profile (AGP). The AGP is produced by a data-analysis software program that aggregates CGM data from several days or weeks to statistically and visually characterize glycemic exposure, variability, stability, and time in target range (TIR), thus enabling clinicians and patients to discern patterns of glycemic variation and unrecognized hypoglycemia and make pharmacologic and lifestyle adjustments accordingly (**FIGURE 1**).[2,21]

The AGP operates on the principle that in the management of diabetes, more glucose data is better than less when it is presented in a format that can be easily and readily actionable as it provides a more accurate picture about what and where therapy should be adjusted. The AGP program, developed by Mazze et al, in collaboration with the International Diabetes Center in Minneapolis, Minnesota, is a non-proprietary open-source program licensed to device manufacturers for inclusion in their software packages that can read data from any CGM device, regardless of the manufacturer, as well as SMBG monitor downloads.[1,22] It is recommended that 14 days of CGM data be collected for an accurate, comprehensive analysis of key glucose metrics by AGP.[2]

The AGP provides unique insights into several areas regarding diabetes pathophysiology and management that are not available with HbA1c: (1) the glucose perturbations that underlie the diagnosis of diabetes; (2) the underlying dysglycemia as a basis for selection and/or initiation of targeted therapy; and (3) whether current therapy is efficacious and, if not, what therapeutic or behavioral approach would likely provide better control. Consequently, AGP provides a better basis than HbA1c for decision-making regarding the dosage and timing of therapies in individual patients. AGP has been used in clinical trials in conjunction with CGM to characterize the impact of medications on the diurnal glucose profile.[23-25] In clinical practice in the United States, AGP is being used in some centers to assist in glycemic control.

An important component of AGP is the standardization of clinical terms and key metrics that was developed with input from an expert panel of US diabetes specialists.[2,14] These terms and metrics include:[2]

1. Default blood glucose target range: 70-180 mg/dL
2. TIR (expressed as percentage of readings in range and hours per day in range)
3. Glucose exposure (expressed as mean glucose of all readings, and estimated HbA1c based on average glucose and area under the median curve)
4. Glycemic variability (expressed as standard deviation [SD], coefficient of variation, and interquartile range [IQR])
5. Hypoglycemia: <70 mg/dL, <60 mg/dL, and <50 mg/dL corresponding to low, very low, or dangerously low glucose levels, respectively
6. Hyperglycemia: >180 mg/dL, >250 mg/dL, and >400 mg/dL corresponding to high, very high, or dangerously high glucose levels, respectively
7. Estimated HbA1c is based on the mean glucose for the period under investigation.*

*Since the formula for the estimated HbA1c uses all of the captured glucose values, when subjects have a significant number of glucose values in the hypoglycemic range, the estimated HbA1c will be lower than the measured laboratory HbA1c value.

The default page of the software program is the "dashboard," which presents the most relevant graphical and statistical information to facilitate rapid assessment of the patient's glycemic condition so that the provider can make timely clinical decisions. The patient can view the dashboard simultaneously with the provider, when possible, so that the patient can provide relevant insights and feedback.[2] The dashboard is composed of 3 parts: (1) statistical summary, (2) visual display, and (3) daily views. The statistical summary includes *glucose exposure* (average glucose and estimated HbA1c based on collected data), *glucose variability* (total SD and IQR of collected data), *glucose ranges* (percentages of values in target range; low, very low, and dangerously low; and high, very high, and

FIGURE 1A Daily ambulatory glucose profile reports over a 6-day period

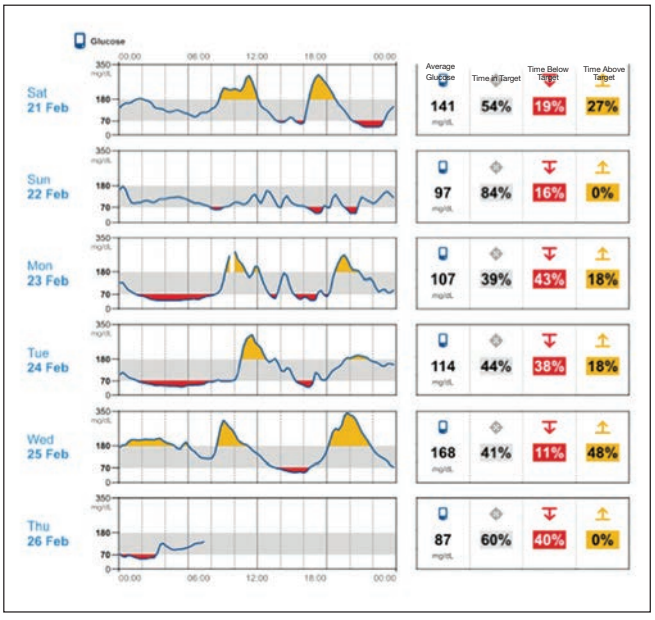

FIGURE 1B Daily patterns with ambulatory glucose profile over 14 days

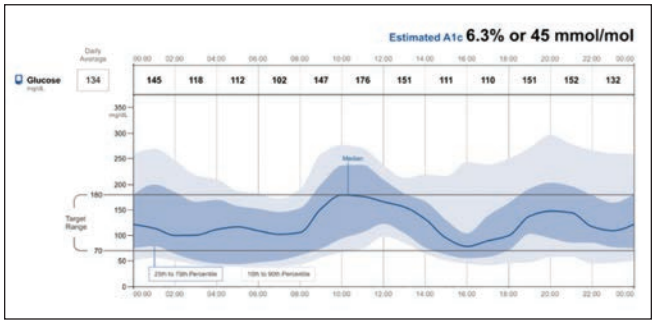

Figure 1a and 1b. The ambulatory glucose profile (AGP) operates on the principle that in the management of diabetes, more glucose data is better than less when it is presented in a format that can be easily and readily actionable. The AGP aggregates glucose data over multiple days to help the patient and providers discern patterns of glycemic variation and unrecognized hypoglycemia. The AGP can take data from several sources to include SMBG monitor downloads to CGM glucose data.

Figure 1a: Daily AGP reports over a 6-day period.

Figure 1b: AGP report that aggregates 14 days of daily AGP reports over a 24-hour period displayed by time to show the spread of glucose values within each time interval. The dark blue line is the median curve (50th percentile) and shows the median glucose value for each time point. The darker blue shaded area represents the interquartile range (IQR). The light blue shaded area represents the outlier values (lowest and highest 10%).

Images courtesy of Dr. Roger Mazze.

dangerously high ranges), and *data sufficiency* (average number of tests per day upon which the data were generated).[2] An expanded statistical view can be accessed with one click that provides more detailed data regarding these variables.

The visual display section of the AGP dashboard presents a modal day (standard or average day) that is derived by collapsing and plotting according to time (without regard to date) all data collected over multiple days as if they occurred over 24 hours. This is displayed as smoothed curves representing the median (50th), 25th to 75th frequency percentile, and 10th to 90th frequency percentile (**FIGURE 1B**). The median curve is a representation of glucose stability, while the 25th to 75th percentile curve defines the IQR, representing glucose variability, and the 10th to 90th percentile curve tracks glucose excursions.[14] One can easily see the times of day when glucose is most consistently high or low, when the greatest variability occurs, and the magnitude of that variability. For example, the 10th to 90th percentile curve crossing 70 mg/dL or lower at a given time of day indicates a moderate risk of hypoglycemia at that time since 10% of values fall in that range, while the 25th to 75th percentile curve crossing that threshold indicates a greater risk since 25% of values fall into the hypoglycemia range at that time.[2]

The daily view section of the AGP dashboard consists of a calendar of thumbnail AGPs (target range and median line) of the 24-hour pattern for each day included in the overall profile. This simplifies comparison of patterns on specific days (eg, weekday vs weekend) and facilitates conversations with patients to discern circumstances that might be contributing to glucose variability or excursions.[2]

Obviously, information about the patient's treatment regimen, adherence, and food intake must be considered in conjunction with the AGP. Currently, the clinician can add such information on the AGP modal day graphic at a clinic visit.[2]

The AGP provides insight into glycemic variability and hypo- and hyperglycemic excursions that are not possible based solely on HbA1c. In **FIGURES 2A** and **2B,** two subjects have similar HbA1c values (7.4% and 7.8%), but very different daily glycemic patterns. In fact, the patient with the HbA1c of 7.4% has poorer glycemic control in terms of markedly greater blood glucose variability throughout the day, instances of hypoglycemia midday, with several glucose excursions well above 250 mg/dL. The patient with the HbA1c of 7.8% has much less glycemic variability, fewer hyperglycemic excursions above 250 mg/dL, and no instances of hypoglycemia.

CONCLUSION

Glycemic variability is increasingly recognized as an important measure of glycemic control, and its minimization an important treatment goal. CGM provides a comprehensive

FIGURE 2A Daily patterns with ambulatory glucose profile over 9 days

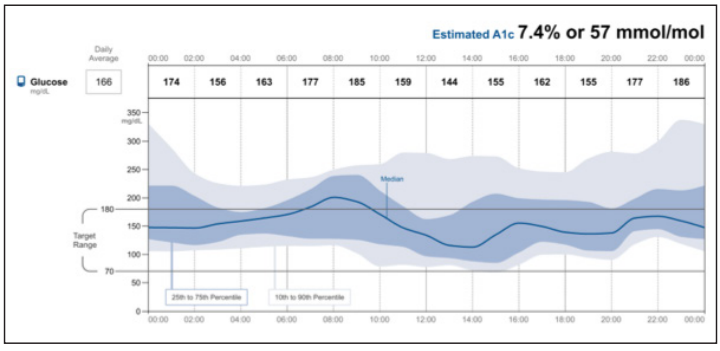

FIGURE 2B Daily patterns with ambulatory glucose profile over 15 days

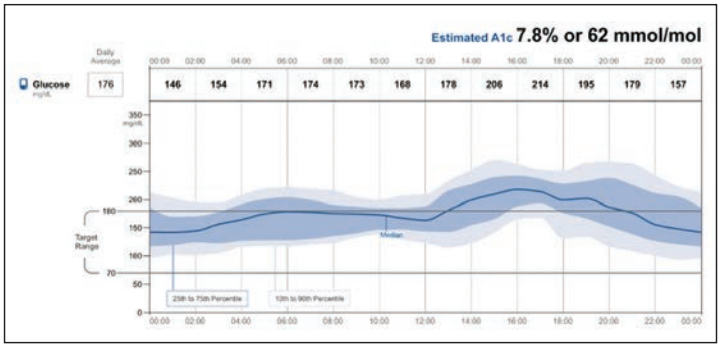

Figure 2a and b. Two patients with similar HbA1c values, but very different daily glycemic patterns.

Figure 2a: Patient with a slightly lower HbA1c has poorer glycemic control in terms of markedly greater blood glucose variability throughout the day, instances of hypoglycemia midday, and several glucose excursions well above 250 mg/dL throughout the day.

Figure 2b: The patient has a slightly higher HbA1c, but much less glycemic variability, fewer hyperglycemic excursions above 250 mg/dL, and no instances of hypoglycemia.

Images courtesy of Dr. Roger Mazze.

view of a patient's glucose levels. However, the amount of data generated can become unmanageable, and there is no standardization among the 3 CGM manufacturers regarding software or report output. Ambulatory glucose profile (AGP) is a data-analysis software program that facilitates the aggregation of CGM data into actionable information by statistically and visually characterizing glycemic exposure, variability, stability, and time in target range. This allows easier discernment of glycemic patterns to inform decisions regarding pharmacologic and lifestyle management. ●

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Innovations in Insulin for Type 2 Diabetes Mellitus

John E. Anderson, MD

INTRODUCTION

The treatment of individuals with type 2 diabetes mellitus (T2DM) has benefited from several new medications, delivery devices, and monitoring methods. Treatment recommendations and algorithms have evolved to integrate these new medications, including glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium glucose cotransporter-2 inhibitors.[1-3] These algorithms also reaffirm the key role for insulin, particularly basal insulin, across the spectrum of T2DM management.

Given this key role for insulin, it is vitally important that provider and patient barriers to insulin therapy are addressed. For providers, becoming familiar with treatment advances and recommended algorithms can address some barriers, while practice redesign with greater involvement of other members of the health care team and office staff can ease time and resource limitations.[4] Similarly, many patient barriers can be resolved through greater engagement and a shared role in decision making.[5]

A factor contributing to the key role of insulin in T2DM management is the continued improvements in pharmacokinetics and pharmacodynamics to more closely mimic endogenous insulin. Basal insulin analogs are more likely to provide 24-hour coverage with once-daily dosing than neutral protamine Hagedorn (NPH) insulin.[6] Insulin analogs are generally preferred over human insulins because of a lower incidence of hypoglycemia with insulin analogs.[3] Despite their benefits, insulin analogs are limited by pharmacodynamic profiles that do not exactly mimic endogenous glucose release. Thus, dose time inflexibility and the need for twice daily dosing for basal insulin remain problematic for some patients. Moreover, hypoglycemia, particularly nocturnal hypoglycemia, and uncontrolled hyperglycemia remain concerns with insulin analogs, although less so than with human insulins.[7]

Shortcomings of existing insulin analogs have led to further development of new insulin formulations. Insulin glargine 300 units/mL and inhaled rapid-acting human insulin were recently approved by the US Food and Drug Administration (FDA), while other basal and prandial insulins are in late-stage development in the United States, with some such as insulin degludec approved in other countries.

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DISCLOSURES

Dr. Anderson discloses that he is on the advisory board and speakers' bureau for Abbott Laboratories; AstraZeneca; Boehringer Ingelheim GmbH; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; and Sanofi US. Editorial support in the preparation of this article was provided by Gregory Scott, PharmD, RPh, and supported by Sanofi US. The author was responsible for all content and editorial decisions and received no honoraria related to the development/presentation of this article.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from Sanofi US.

INNOVATIONS IN INSULIN

Recently approved in the United States

Insulin glargine 300 units/mL

Insulin glargine 300 units/mL (Gla-300) (Toujeo) is a more concentrated formulation (same number of units in one-third the volume) of the basal insulin analog glargine 100 units/mL (Gla-100) (Lantus), which leads to important pharmacokinetic and clinical differences that translate into a different clinical profile (**TABLE 1**). The pharmacokinetic profile of Gla-300 demonstrates a more prolonged and flatter profile (ie, lower peak-to-trough difference) of the active M_1 moiety compared with Gla-100.[8] Following a dose of 0.4 units/kg, the elimination half-life of Gla-300 was 21.2 hours compared with 14.9 hours for Gla-100.[8]

Efficacy and safety

The differences between Gla-300 and Gla-100 were identified from analyses of the EDITION program of randomized, placebo-controlled clinical trials. A recently reported meta-analysis of the EDITION 1, 2, and 3 clinical trials compared the efficacy and safety of Gla-300 with Gla-100 in adults with T2DM (N=2496) treated with basal and mealtime insulin, basal insulin and oral glucose-lowering agents, or no prior insulin, respectively, over 6 months.[9] Over the 3 studies, the mean decreases in HbA1c (–1.0% vs –1.0%) and fasting plasma glucose (FPG) (–37 vs –41 mg/dL) were similar in the Gla-300

TABLE 1 Summary of outcomes comparing insulin glargine 300 units/mL with insulin glargine 100 units/mL[9]

Measurement	Outcomes
HbA1c reduction	Gla-300 = Gla-100
Proportion achieving HbA1c <7.0%	Gla-300 = Gla-100
FPG reduction	Gla-300 = Gla-100
Basal insulin dose	Gla-300 > Gla-100
Weight gain	Gla-300 < Gla-100
Confirmed (≤70 mg/dL) or severe hypoglycemia	Gla-300 < Gla-100
Nocturnal confirmed (≤70 mg/dL) or severe hypoglycemia	Gla-300 < Gla-100
Incidence of treatment-emergent adverse events	Gla-300 = Gla-100

Abbreviations: FPG, fasting plasma glucose; Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL.

and Gla-100 groups.[9] Moreover, the proportion of patients who achieved HbA1c <7% after 6 months was similar in the Gla-300 and Gla-100 groups (36.2% vs 35.5%, respectively). The dose of basal insulin increased in both groups, but was 12% higher with Gla-300 than Gla-100 at 6 months (0.85 vs 0.76 units/kg-day, respectively). Weight increased in both groups, but the change in weight was significantly less with Gla-300 than Gla-100 (0.51 kg vs 0.79 kg, respectively; *P*=.039).

In terms of safety, the cumulative number of confirmed (≤70 mg/dL) or severe hypoglycemic events (requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) was 14% lower with Gla-300 than Gla-100, with annualized rates of hypoglycemia at any time of day of 15.22 vs 17.73 events/participant-year, respectively (*P*=.0116).[9] The rates and percentages were similar in people aged ≥65 years and those aged <65 years. Similarly, the cumulative number of nocturnal confirmed (≤70 mg/dL) or severe hypoglycemic events was 31% lower with Gla-300 than Gla-100 with annualized rates of nocturnal events of 2.10 vs 3.06 events/participant-year, respectively (*P*=.0002). A separate post hoc analysis showed that significantly more patients aged 65 years and older treated with Gla-300 rather than Gla-100 achieved HbA1c <7% without nocturnal hypoglycemia (25.5% vs 17.3%, respectively; *P*=.003).[10] No other between-treatment differences in the safety profile were observed, with similar rates of adverse events across all 3 EDITION studies.[9]

A recent network meta-analysis compared the efficacy and safety of Gla-300 with Gla-100, detemir, NPH, degludec, and premixed insulin for T2DM.[11] A network meta-analysis permits inferences into the comparative effectiveness of treatments that may or may not have been evaluated directly against each other in a clinical trial. The network meta-analysis, which included 44 randomized clinical trials, indicated that Gla-300 was associated with comparable glycemic control and weight change to the other basal insulin comparators.[11] In addition, Gla-300 was associated with a significantly lower rate of nocturnal hypoglycemia vs Gla-100 (relative risk: 0.57; 95% confidence interval [CI]: 0.33 to 0.98), NPH (0.21; 0.10 to 0.44), and premixed (0.42; 0.21 to 0.81) insulin. The rate was numerically (but not statistically) lower vs detemir (0.53; 0.28 to 1.01) and degludec (0.68; 0.36 to 1.25).

Patient satisfaction

Patient satisfaction is similar with Gla-300 and Gla-100. In EDITION 1, which compared Gla-300 with Gla-100 in patients previously treated with basal and prandial insulin, satisfaction scores increased similarly from baseline to month 6 in both groups.[12] A similar proportion of participants in the Gla-300 and Gla-100 groups experienced a decrease from baseline to month 6 in the perception of hypoglycemia (59% vs 54%, respectively).

Insulin degludec

Insulin degludec is a basal insulin approved in the United States in September 2015. It is composed of dihexamers that reorganize into long multihexamer chains following subcutaneous administration. These multihexamer chains slowly disassemble and release active insulin monomers that are continuously absorbed into the systemic circulation.[13,14] Euglycemic clamp studies involving the controlled administration of insulin *in vivo* with the administration of glucose adjusted to maintain euglycemia, have demonstrated a duration of action >24 hours.[15] In patients with T2DM, the glucose-lowering effect was found to be evenly distributed over each 6-hour interval for a 24-hour period.[15]

Efficacy and safety

The efficacy and safety of insulin degludec have been established in phase 3, randomized, open-label, clinical trials, with HbA1c reduction similar to Gla-100 over 52 weeks (1.1% vs 1.2%, respectively).[16,17] Across the 2 studies, similar proportions of patients achieved HbA1c <7% with insulin degludec compared with Gla-100 (49% to 52% vs 50% to 54%, respectively). Overall confirmed hypoglycemia occurred with similar frequency in insulin-naïve patients treated with insulin degludec compared with Gla-100 (1.52 vs 1.85 events/patient-year) but less frequently in patients previously treated with insulin (11.09 vs 13.63 events/patient-year; *P*=.0359). Nocturnal confirmed hypoglycemia occurred significantly less frequently with insulin degludec than Gla-100

in both insulin-naïve patients (0.25 vs 0.39 events/patient-year; *P*=.038) and patients previously treated with insulin (1.39 vs 1.84; *P*=.0399).[16,17]

Cardiovascular safety. Approval of insulin degludec in the United States was declined in 2013 by the FDA due to concerns regarding the cardiovascular safety of insulin degludec. Analyses of data from completed phase 3 clinical trials could neither confirm nor exclude increased cardiovascular risk with insulin degludec.[18,19] Consequently, the FDA requested additional cardiovascular outcomes data from a dedicated clinical trial. The DEVOTE trial was started in October 2013 and has recently completed recruitment of patients with T2DM at high risk of cardiovascular events. Interim results of the DEVOTE study have been submitted to the FDA; the study is scheduled for completion in the second half of 2016.[20]

Dose timing

The pharmacokinetic and pharmacodynamic profile of insulin degludec has prompted trials to investigate different dosing time strategies. In one trial, patients with T2DM (N=687) were randomized to insulin degludec administered once daily with the evening meal, insulin degludec once daily with "flex" administration time alternating between morning and evening (creating dosing intervals of 8 to 40 hours), or Gla-100 once daily at the same time each day.[21] After 26 weeks, the HbA1c reduction with insulin degludec (flex) was similar to Gla-100 (–1.28% vs –1.26%, respectively). Fasting plasma glucose reductions were significantly greater with insulin degludec (flex) than Gla-100 (–58 vs –50 mg/dL, respectively; *P*=.04). The rates of overall confirmed hypoglycemia and nocturnal confirmed hypoglycemia were similar in the insulin degludec (flex) and Gla-100 groups.

The 25-hour elimination half-life of insulin degludec prompted a trial investigating the administration of insulin degludec 3 times per week.[15,22] This 26-week trial showed that insulin degludec administered on Monday, Wednesday, and Friday provided inferior glycemic control compared with Gla-100 once-daily. Moreover, the risk of hypoglycemia increased with insulin degludec.

Quality of life

Finally, there is the suggestion that insulin degludec may improve patient quality of life compared with Gla-100. A meta-analysis of 3 treat-to-target trials over 26 to 52 weeks showed significant improvement in several measures of physical and mental health with insulin degludec.[23] However, the open-label nature of the trials must be considered when interpreting these results.

Rapid-acting inhaled recombinant human insulin

Rapid-acting inhaled recombinant human insulin is a dry powder formulation of regular human insulin adsorbed onto Technosphere microparticles for oral inhalation (Afrezza) and was FDA approved in June 2014. Using the breath-actuated device, the dry powder is aerosolized and delivered to the lung.[24] The peak insulin concentration is achieved within 12 to 17 minutes compared with 134 minutes for 10 units of subcutaneously administered regular human insulin.[25] The maximum bioeffect of the rapid-acting recombinant human insulin is dose-dependent, occurring between 42 and 58 minutes for doses of 25, 50, and 100 units, respectively, compared to 171 minutes for regular human insulin.[25]

Efficacy and safety

The efficacy and safety of inhaled rapid-acting human insulin was investigated in patients with T2DM inadequately controlled on metformin or 2 or more oral glucose-lowering agents (N=353).[24] Following a 6-week run-in period, patients were randomized to inhaled rapid-acting human insulin or inhaled placebo. Doses were titrated during the first 12 weeks of the 24-week treatment phase and kept stable for the last 12 weeks. The doses of oral agents were kept stable. At 24 weeks, the mean reductions in HbA1c were –0.82% vs –0.42% in the inhaled rapid-acting human insulin and inhaled placebo patients, respectively (end-of-treatment difference: –0.40; 95% CI: –0.57 to –0.23). The mean change from baseline for FPG was –11.2 mg/dL and –3.8 mg/dL, respectively (95% CI: –18.0 to 3.2). More patients treated with inhaled rapid-acting human insulin achieved HbA1c <7.0% (32.2% vs 15.3%).

Inhaled rapid-acting human insulin has also been investigated as add-on therapy to basal insulin providing similar glycemic control compared to twice-daily premixed biaspart insulin.[26] After 52 weeks, reductions in HbA1c were 0.68% vs 0.76%, respectively. Patients in the group receiving inhaled rapid-acting human insulin had significantly lower weight gain and fewer mild-to-moderate and severe hypoglycemic events but an increased incidence of cough and change in pulmonary function.

The safety of inhaled rapid-acting human insulin has been determined in a pooled analysis of patients with T2DM treated with inhaled insulin (N=1991), placebo (N=290), or unspecified nonplacebo comparators (N=1363).[24] The mean exposure to inhaled rapid-acting human insulin was 8.18 months. Common adverse events (inhaled rapid-acting human insulin vs placebo vs nonplacebo comparator) were: cough (25.6% vs 19.7% vs 5.4%); throat pain or irritation (4.4% vs 3.8% vs 0.9%); headache (3.1% vs 2.8% vs 1.8%); diarrhea (2.7% vs 1.4% vs 2.2%); productive cough (2.2% vs 1.0% vs

0.9%); fatigue (2.0% vs 0.7% vs 0.6%); and nausea (2.0% vs 0.3% vs 1.0%).

In a placebo-controlled study of patients with T2DM (N=353), nonsevere hypoglycemia occurred in 67% of patients treated with inhaled rapid-acting human insulin compared with 30% treated with inhaled placebo.[24] Severe hypoglycemia (event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose value consistent with hypoglycemia or prompt recovery after treatment for hypoglycemia) occurred in 5.1% and 1.7%, respectively.

Pulmonary function decline has been investigated in clinical trials lasting up to 2 years that excluded patients with chronic lung disease.[24] Patients treated with inhaled rapid-acting human insulin had a 40 mL greater decline from baseline in forced expiratory volume in 1 second (FEV_1) compared to patients treated with comparator glucose-lowering treatments. (The average total lung capacity in a healthy, young adult is approximately 4-6 L.[27]) The decline occurred during the first 3 months of therapy and persisted over 2 years but did not progress. A decline in FEV_1 ≥15% occurred in 6% of patients treated with inhaled rapid-acting human insulin compared with 3% of patients treated with comparator agents.[24] Investigation of potential lung disease, including the use of spirometry, is advised prior to initiating inhaled rapid-acting human insulin.

Basal insulins in late-stage development

Pegylated insulin lispro

Pegylated insulin lispro is a rapid-acting insulin analog with a hydrodynamic size that is 4 times that of insulin lispro, resulting in slowed subcutaneous absorption and a significantly longer duration of action than insulin lispro.[28] In patients with T2DM, the elimination half-life ranged from 44.7 hours to 75.5 hours. The peak-to-trough fluctuation was <2, demonstrating a relatively peakless blood level at steady state.[29]

Currently available data are limited to preliminary reports of results from phase 3 studies, which show pegylated insulin lispro has superior glucose-lowering efficacy compared with Gla-100 in patients with T2DM.[30-32] Patients treated with pegylated insulin lispro experienced significantly lower rates of nocturnal hypoglycemia than patients treated with Gla-100 and comparable to significantly less weight gain.[30-32] More patients achieved HbA1c <7% without nocturnal hypoglycemia over 26 or 52 weeks with pegylated insulin lispro.[31,32] Pegylated insulin lispro was associated with a similar or lower total hypoglycemia rate and higher basal insulin dose.[31,32] Triglycerides were similar or higher with pegylated insulin lispro, but low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were similar or lower than with Gla-100.[31,32] Pegylated insulin lispro was associated with an increase in liver fat content from baseline to 26 weeks, but stabilized from weeks 26 to 52.[32]

Post hoc analyses of phase 2/3 trials also show similar effects on cholesterol and liver fat. In one analysis, pegylated insulin lispro was associated with changes in HDL-C (0 to –5 mg/dL) and LDL-C (0 to 7 mg/dL) over 26 weeks.[33] In another analysis, pegylated insulin lispro was associated with a significant increase in liver fat content, with a mean change from baseline of –1% to 5% compared with –4% to 0% with Gla-100 (P≤.002) at 26 and 52 weeks in both type 1 and type 2 diabetes.[34]

Insulin lispro protamine

Insulin lispro protamine, a component of premix Humalog, is, by itself, an intermediate-acting blood glucose lowering agent that is produced by combining insulin lispro and protamine sulfate under appropriate conditions for crystal formation.

The pharmacokinetics and pharmacodynamics of insulin lispro protamine were investigated in a 5-arm crossover euglycemic clamp study in patients with T2DM.[35] Results showed that the duration of action of insulin lispro protamine 0.8 units/kg was longer than 23 hours, which was similar to Gla-100 and insulin detemir.[35] The onset of exposure and time to reach 50% maximum concentration were significantly earlier with insulin lispro protamine compared with Gla-100 and insulin detemir.

The efficacy and safety of insulin lispro protamine has been investigated in 4 randomized, open-label, parallel-group trials as add-on therapy to oral agents (1 study also included exenatide) over 24 to 36 weeks. The mean reduction in HbA1c and the proportion of patients who achieved HbA1c <7% were similar for insulin lispro protamine and comparators (Gla-100 and insulin detemir).[36-39] Overall hypoglycemia rates were similar for insulin lispro protamine and Gla-100, but were significantly higher for insulin lispro protamine compared with insulin detemir.[36-39] Rates of nocturnal hypoglycemia were comparable or higher with insulin lispro protamine than Gla-100, and were significantly higher for insulin lispro protamine than insulin detemir.[36-39] Weight gain was similar for insulin lispro protamine and Gla-100, but significantly greater for insulin lispro protamine than insulin detemir.[36,37,39]

Prandial insulin in late-stage development

Faster-acting aspart

Faster-acting insulin aspart contains insulin aspart with 2 excipients, nicotinamide and arginine, that result in a stable

TABLE 2 **Unmet clinical needs addressed by insulins recently approved or in late-stage development**

Insulin	Unmet clinical need addressed
Insulin glargine 300 units/mL	Hypoglycemia, particularly nocturnal; twice-daily dosing
Inhaled rapid-acting recombinant human insulin	Needle phobia; glycemic variability; ease of mealtime dosing
Insulin degludec	Nocturnal hypoglycemia; twice-daily dosing; dosing time inflexibility
Pegylated insulin lispro	Nocturnal hypoglycemia; glycemic variability; twice-daily dosing
Insulin lispro protamine	To be determined
Faster-acting insulin aspart	Ease of mealtime dosing

formulation and faster initial absorption than insulin aspart following subcutaneous injection. In a randomized, double-blind, crossover study, faster-acting insulin aspart was found to have a 57% faster onset of exposure (4.9 vs 11.2 minutes; 95% CI: 0.36, 0.51) and 35% earlier time to reach 50% maximum concentration (20.7 vs 31.6 minutes; 95% CI: 0.59, 0.72) than insulin aspart.[40] The area under the serum insulin aspart curve was 4.5-fold greater with faster-acting insulin aspart during the first 15 minutes. Both treatments had a similar maximum blood concentration, time to maximum blood concentration, and total exposure. Faster-acting insulin aspart had a significantly greater glucose-lowering effect within 90 minutes after dosing, although both had similar total and maximum glucose-lowering effects.

SUMMARY

Insulin formulations have undergone significant improvements in recent decades. While insulin is a recommended treatment option across the spectrum of treatment for patients with T2DM, unmet clinical needs remain. Three insulin formulations were recently approved in the United States and others are in late-stage development with features that address one or more of these unmet clinical needs (**TABLE 2**). ●

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Role of the Kidney and SGLT-2 Inhibition in Type 2 Diabetes Mellitus

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INTRODUCTION

The pathophysiology of type 2 diabetes mellitus (T2DM) involves a complex interaction of several defects, with insulin resistance in muscle and a progressive decline in pancreatic β-cell function playing central roles.[1-3] Other defects include increased release of glucose by the liver and glucagon by the pancreatic islet α-cells, impairment of the incretin system in the gastrointestinal tract, and amplified adipocyte lipolysis.[1] An increased renal threshold for glucose excretion also was recognized as a defect in T2DM more than 6 decades ago.[4] Identifying that the kidney plays a key role in glucose homeostasis has led to the development of therapeutic agents that target mechanisms within the kidney.

ROLE OF THE KIDNEY IN GLUCOSE HOMEOSTASIS

Influenced by hormonal and neural factors, a key function of the kidneys is to filter the plasma while removing or reducing the concentration of solutes such as glucose.[5] In persons without diabetes, much of the 160 to 180 g of glucose that is filtered each day by the kidneys is reabsorbed in the proximal tubule, principally the early convoluted segment of the proximal tubule.[5,6] Reabsorption across the kidney membrane is mediated through the action of sodium glucose cotransporters (SGLTs), whereas glucose reabsorption into the circulation is mediated by glucose transporters (GLUTs). Most glucose reabsorption in the kidney (approximately 90%) is mediated by the high-capacity, low-affinity SGLT-2. The remaining 10% of glucose that is reabsorbed occurs in the more distal segment of the proximal tubule through the action of the low-capacity, high-affinity SGLT-1.[6,7]

In individuals without diabetes, little or no glucose appears in the urine when plasma glucose remains below ~180 mg/dL.[8] The picture is quite different in T2DM, where the plasma glucose concentration and, consequently, the amount of glucose presented to the kidneys are increased. The renal threshold of glucose rises, however, and the capacity of the kidney to reabsorb glucose also increases.[9] Unless plasma glucose exceeds approximately 240 mg/dL, as it may in poorly controlled diabetes, glucosuria generally is not evident.[8] The reason for the increased renal threshold for glucose in T2DM is not known, but it may involve upregulation of SGLT-2 mRNA and protein.[9,10]

Another difference exists between healthy individuals and those with T2DM. In healthy fasting individuals, the kidney contributes approximately 20% to 25% of the glucose released into the circulation via renal gluconeogenesis.[6,11] In individuals with T2DM, the kidney's contribution may increase by as much as 300%.[6] Together, these findings demonstrate that the kidneys play a key role in glucose homeostasis and contribute to the pathophysiologic process of hyperglycemia in patients with diabetes.[7]

Sodium glucose cotransporters

SGLT-1 and SGLT-2 have been the most extensively studied of the sodium glucose cotransporters. In addition to the distal segment of the proximal renal tubule, SGLT-1 is found in the small intestine, trachea, heart, brain, testis, and prostate tissue.[12] SGLT-2 is found primarily in the luminal membrane of the S1 and S2 early segments of the proximal renal tubule, where most glucose reabsorption occurs.[13] Its more limited location in the proximal tubule makes SGLT-2 a useful target to influence glucose reabsorption. Moreover, this action is independent of insulin.

This article reviews the role of the available SGLT-2 inhibitors—canagliflozin, dapagliflozin, and empagliflozin—in the management of T2DM as recommended in current guidelines. Results of phase 3 clinical trials are provided, focusing on canagliflozin as a representative of the class.

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DISCLOSURES

Both Dr. Kevin Miller and Dr. Eden Miller disclose that they are on the advisory board and speakers' bureau for Janssen Pharmaceuticals, Inc.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from Janssen Pharmaceuticals, Inc.

Suggestions also are provided to facilitate the integration of SGLT-2 inhibitors into clinical practice.

SGLT-2 inhibition with canagliflozin has been shown to lower the renal threshold for glucose excretion to approximately 60 mg/dL in healthy individuals and to approximately 70 to 90 mg/dL in individuals with T2DM.[6] Corresponding threshold levels with dapagliflozin were 37 mg/dL and 21 mg/dL, respectively.[9] The amount of glucose excreted in the urine per day is increased by approximately 70 g with dapagliflozin and empagliflozin and 100 g with canagliflozin.[14-16]

ROLE OF THE SGLT-2 INHIBITORS IN T2DM

The SGLT-2 inhibitors' insulin-independent mechanism of action enables their use at any stage of T2DM. Each of the available SGLT-2 inhibitors has been approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.[14-16] Guidelines from the 2015 American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and 2015 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend SGLT-2 inhibitors in combination with other glucose-lowering agents for dual or triple therapy.[17-19] In the ADA/EASD guidelines, the SGLT-2 inhibitors represent 1 of 6 classes of medications recommended for use in combination with metformin or metformin plus 1 other agent.[17] In the AACE/ACE algorithm, the SGLT-2 inhibitor class is positioned as the first class of oral agents for use as monotherapy (as an alternative to metformin) or for use in combination with metformin or metformin plus 1 other agent.[19] **TABLE 1** summarizes the effects of SGLT-2 inhibitors.[17]

Experience with SGLT-2 inhibitor therapy

Glycemic and nonglycemic effects

Each of the SGLT-2 inhibitors has been investigated in randomized, double-blind, placebo-controlled, multicenter trials. Whether as monotherapy or as add-on therapy to metformin, short-term use of each of the SGLT-2 inhibitors at approved doses reduces the HbA1C approximately 0.3% to 1.2% and the fasting plasma glucose 12 to 36 mg/dL relative to placebo.[20-25] Limited data suggest a pronounced effect on postprandial glucose, with a reduction of 43 to 59 mg/dL. Body weight and systolic blood pressure also are reduced, ranging from 2.1 to 4.0 kg and 2.1 to 5.2 mm Hg, respectively.[20-25] Glycemic and nonglycemic benefits generally have been sustained in studies up to 104 weeks in duration. [20-38] The influence of baseline HbA1C on HbA1C efficacy is consistent with results observed with other glucose-lowering agents.[39] A detailed review of phase 3 clinical trials with the 3 SGLT-2 inhibitors has been published by Nauck.[40]

As expected because of their unique mechanism of glucose lowering, the SGLT-2 inhibitors are effective as part of dual or triple combination therapy, including insulin.[26-28,31,41-48] In selected patients who do not achieve an adequate response to basal-bolus insulin therapy, the addition of an SGLT-2 inhibitor may further improve glycemic control and reduce the amount of insulin required, particularly in highly insulin-resistant patients.[17,48]

Safety and tolerability

The increased urinary excretion of glucose that contributes to reductions in plasma glucose, body weight, and blood pressure also may contribute to adverse events observed with SGLT-2 inhibitors. These include genital mycotic infections, urinary tract infections, and adverse events related to osmotic diuresis (pollakiuria), polyuria, and volume depletion.[49,50] Modest, transient decreases in glomerular filtration rate (3% to 10%) also have been observed.[49,50] These changes in the glomerular filtration rate (GFR) migrated back to baseline by 52 weeks.

The safety of canagliflozin, dapagliflozin, and empagliflozin has been shown to be generally similar in pooled analyses of phase 3 trials.[16,49,50] The pooled analysis of canagliflozin included four 26-week placebo-controlled trials as monotherapy or in combination with metformin-based treatment (N=2313).[49] The incidence of adverse events related to study drug was similar among patients treated with canagliflozin 100 mg and 300 mg and placebo (60.1% vs 59.2% vs 59.4%, respectively). A serious adverse event was experienced by 3.4% of patients in each of the canagliflozin groups and 2.6% of patients treated with placebo. Of particular interest, incidences of adverse events associated with canagliflozin 100 mg vs canagliflozin 300 mg vs placebo were:

- genital mycotic infection/female (10.4% vs 11.4% vs 3.2%)
- genital mycotic infection/male (4.2% vs 3.7% vs 0.6%)
- urinary tract infection (5.9% vs 4.3% vs 4.0%)
- osmotic diuresis-related (6.7% vs 5.6% vs 0.8%)
- volume depletion-related (1.2% vs 1.3% vs 1.1%).

With canagliflozin as monotherapy or as add-on therapy to metformin, the incidence of hypoglycemia is generally less than 4% and similar to placebo, with infrequent cases of major or severe hypoglycemia.[20-28]

As with other glucose-lowering agents, use of SGLT2 inhibitors with insulin and/or a sulfonylurea is associated with an increased risk of hypoglycemia.[49,50] In patients not receiving background sulfonylurea therapy, any documented hypoglycemia occurred in 3.8% and 4.3% of patients treated with canagliflozin 100 mg or 300 mg, respectively, and 2.2% of patients treated with placebo. In patients receiving background sulfonylurea therapy, the rates were 27.4%, 30.1%, and 15.4%, respectively.

TABLE 1 **Effects of SGLT-2 inhibitors in the management of T2DM[17]**

Parameter	Effect of SGLT-2 inhibitors
HbA1C	0.5% to 1.2% reduction (compared with placebo)
Glucose-lowering actions dependent on insulin secretion?	No
Weight	~2 kg weight loss, stabilizing over 6-12 months
Blood pressure	~2-4/~1-2 mm Hg reduction
Low-density lipoprotein cholesterol	~5% increase
Plasma uric acid level	Reduction
Albuminuria	Reduction
Serum creatinine	Increase (transient)
Microvascular outcomes	Effect unknown

Abbreviations: HbA1C, glycosylated hemoglobin; SGLT-2, sodium glucose cotransporter-2; T2DM, type 2 diabetes mellitus.

TABLE 2 **Selected postmarketing studies required by US Food and Drug Administration[51-53,a]**

Purpose	Canagliflozin	Dapagliflozin	Empagliflozin
Cardiovascular outcomes	X	X	X
Cancer		Bladder	Breast, bladder, lung, melanoma
Bone safety	X		X
Pediatrics	X	X	X
Other			Liver toxicity, kidney toxicity, complicated genital infections, complicated urinary tract infections, hypersensitivity reactions, events related to hypovolemia
Pharmacovigilance	Malignancies, serious pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities, pregnancy outcomes	Liver abnormalities, pregnancy outcomes	

[a]Some of the studies are required of all medications approved for diabetes, whereas others are required to clarify possible safety signals observed in animal studies or clinical trials in humans.

Pooled analyses showed an increase in the low-density lipoprotein cholesterol (LDL-C) for all 3 SGLT-2 inhibitors. For canagliflozin, mean placebo-subtracted increases of 4.5 mg/dL and 8.0 mg/dL for canagliflozin 100 mg and 300 mg, respectively, were observed.[49] Changes in total cholesterol (3.4% vs 5.2% vs 0.9%), non-high-density lipoprotein cholesterol (2.2% vs 4.3% vs 0.7%), high-density lipoprotein cholesterol (HDL-C) (9.4% vs 10.3% vs 4.0%), and triglycerides (2.4% vs 0% vs 7.6%) also were observed for canagliflozin 100 mg and 300 mg vs placebo, respectively. For dapagliflozin 10 mg vs placebo, the mean changes from baseline to week 24 were 1.0% to 1.4% vs –0.4% for total cholesterol, 0.6% to 2.7% vs –1.9% for LDL-C, 3.8% to 6.5% vs 3.8% for HDL-C, and –3.2% to –5.4% vs –0.7% for triglycerides, respectively.[50] For empagliflozin 10 mg and 25 mg, increases in LDL-C were 4.6% and 6.5%, respectively, compared with 2.3% for placebo.[16]

The US Food and Drug Administration requires postmarketing studies for each of the 3 SGLT-2 inhibitors (**TABLE 2**).[51-53] Some of these studies are required of all medications approved for diabetes, whereas others are required to clarify possible safety signals observed in animal studies or clinical trials in humans.

Use in chronic kidney disease

Chronic kidney disease (CKD), a common complication in T2DM, presents treatment challenges with SGLT-2 inhibitors because of the drugs' mechanism of action within the kidney. The use of SGLT-2 inhibitors has been assessed in patients with CKD, with mixed efficacy results. Treatment is limited to patients with an estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2 for canagliflozin and empagliflozin, and ≥60 mL/min/1.73 m^2 for dapagliflozin (**TABLE 3**).[14-16]

INTEGRATING SGLT-2 INHIBITOR THERAPY INTO CLINICAL PRACTICE

The unique clinical pharmacology of the SGLT-2 inhibitors avoids some of the challenges associated with other glu-

TABLE 3 Steps prior to initiating or during treatment with SGLT-2 inhibitors[14-16]

	Canagliflozin	Dapagliflozin	Empagliflozin
Prior to initiation, consider:			
Cancer	—	• Avoid in active bladder cancer • Use with caution if history of bladder cancer	—
Cardiovascular status	• Assess volume status; correct hypovolemia in renal impairment, elderly, low SBP, or use of diuretics, ACEI, or ARB		
Drug interactions	• Consider lowering dose of insulin, insulin secretagogue • See package inserts for other drug interactions		
Hepatic function	• Not recommended in severe hepatic impairment	• Assess benefit-risk in severe hepatic impairment	• May be used in hepatic impairment
Pregnancy/nursing	• Use in pregnancy only if potential benefits justify potential risk to fetus • Discontinue nursing or drug during nursing		
Renal function	• Do not initiate if eGFR <45 mL/min/1.73 m^2 • Limit dose to 100 mg/d if eGFR 45 to <60 mL/min/1.73 m^2	• Do not initiate if eGFR <60 mL/min/1.73 m^2	• Do not initiate if eGFR <45 mL/min/1.73 m^2
During treatment, monitor:			
Cardiovascular status	• Signs/symptoms of hypotension • LDL-C		
Electrolytes	• K^+ in impaired renal function and if predisposed to hyperkalemia		
Glucose	• Use glucose tests other than urine glucose and 1,5-anhydroglucitol assay		
Infection	• Genital mycotic infection, urinary tract infection		
Renal function	• eGFR (frequently if <60 mL/min/1.73 m^2); discontinue if persistently <45 mL/min/1.73 m^2	• eGFR; discontinue if persistently <60 mL/min/1.73 m^2	• eGFR (frequently if <60 mL/min/1.73 m^2); discontinue if persistently <45 mL/min/1.73 m^2

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

cose-lowering agents but requires that some steps be taken prior to initiation or during treatment (**TABLE 3**). Because SGLT-2 inhibitors promote osmotic diuresis, adequate renal function is needed; consequently, renal function must be assessed prior to and during treatment with a SGLT-2 inhibitor. In addition, the osmotic diuresis may cause volume depletion with associated signs and symptoms, including hypotension.

Orthostatic hypotension is most common in the first 3 months of therapy.[54] Patients, therefore, must be educated about the signs and symptoms of hypotension. SGLT-2 inhibitors, particularly at higher doses, should be used cautiously with concomitant diuretic therapy, in patients with tenuous intravascular volume status, or in the elderly.[17]

Patients also should be educated about the possibility of genital mycotic infections and urinary tract infections, and to seek medical care should relevant signs or symptoms occur. Patients with a history of a genital mycotic infection and uncircumcised men are at increased risk of a genital mycotic infection.

SUMMARY

SGLT-2 inhibitors provide a complementary mechanism of glucose lowering and can be used as monotherapy or in combination with other medications, including insulin. In addition to improved glycemic control, which generally is maintained over 2 years, SGLT-2 inhibitors provide reductions in body weight and systolic blood pressure. Increases in LDL-C and HDL-C also have been observed. A requirement for adequate renal function is a limitation in patients with CKD. A low incidence of hypoglycemia, ability to promote weight loss, and availability as an oral formulation diminish common barriers to glucose-lowering therapy. ●

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Considerations in the Selection of Antihyperglycemic Therapy for Older Patients With Type 2 Diabetes Mellitus: A Focus on Newer Therapies

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ABSTRACT

Treatment of type 2 diabetes mellitus (T2DM) in older patients is complicated by a variety of factors and requires an individualized approach. Benefits of intensive glycemic control must be weighed against associated risks. Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors are newer antihyperglycemic agents that effectively lower glycated hemoglobin levels, with a low risk of hypoglycemia, and have a neutral or beneficial effect on weight. The purpose of this review is to discuss challenges in treating older patients with T2DM, and the efficacy and safety of these newer classes based on clinical trials in older populations.

INTRODUCTION

In the United States, it is estimated that of adults with diabetes aged 20 years and older, those 65 years of age and older have the highest prevalence of disease (26%).[1] Type 2 diabetes mellitus (T2DM) accounts for the majority of diagnosed cases.[1] In older patients, T2DM is especially concerning because of prevalent comorbid conditions such as renal dysfunction and cardiovascular (CV) disease, which can complicate treatment and are associated with poorer glycemic control.[2] Mortality has also been reported to be 9.2% higher in older patients with T2DM versus without T2DM, likely due to the increased prevalence of microvascular and macrovascular complications.[3]

Individualized treatment is a cornerstone of diabetes care.[4] Recommended glycemic targets for older adults in current diabetes guidelines are summarized in **TABLE 1**.[4-8] It is important to recognize that the older population is heterogeneous, as the spectrum of health status among older patients can range from having no significant health concerns besides T2DM to having several comorbidities that require multiple drugs and challenging treatment regimens. Treatment strategies may therefore differ between older patients with newly developed disease, those with long-standing but well-controlled disease, and those with disease that has been uncontrolled for some time. The variety of individual factors in older patients may not only require less stringent glycemic targets, but also affect choice of antihyperglycemic medication.

Managing older patients with T2DM must include a careful analysis of several confounding factors. The purpose of this review is to discuss treatment considerations in older patients and, in particular, the utility of newer drug classes: dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors.

TREATMENT CONSIDERATIONS FOR OLDER PATIENTS

Hypoglycemia

The risk of hypoglycemia is arguably the most important factor to consider when treating T2DM in older patients, and there is an acknowledged need for better monitoring of glycemia in this population.[9] Hypoglycemia is often

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DISCLOSURES

Dr. Freeman discloses that he is on the speakers' bureau for AstraZeneca; Boehringer-Ingelheim GmbH; Bristol-Myers Squibb Company; Eli Lilly and Company; GlaxoSmithKline; Merck & Co. Inc.; and Novo Nordisk Inc.

ACKNOWLEDGMENT

Medical writing support was provided by Nicole Strangman, PhD, Judy Fallon, PharmD, and Meg Shurak, MS, Complete Healthcare Communications, Inc, Chadds Ford, PA, and funded by Bristol-Myers Squibb and AstraZeneca.

Bristol-Myers Squibb and AstraZeneca funded editorial support for the manuscript, participated in initial discussions of the manuscript scope, and made suggestions for revision. Final approval and decision to submit to the *Journal of Family Practice* for publication were made independently by J. Freeman.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from AstraZeneca.

TABLE 1 Recommended glycemic targets for older adults

Organization	HbA1c goal	Health status
American Diabetes Association[4]	<7.5%*	Otherwise healthy, few comorbidities, no cognitive/functional impairment
	<8.0%*	Multiple comorbidities, ADL impairments, mild-to-moderate cognitive impairment
	<8.5%*	Long-term care, end-stage chronic illness, ADL dependencies, cognitive impairment
American Association of Clinical Endocrinologists[6]	≤6.5%*	Most adults
	7% to 8%†	History of severe hypoglycemia, limited life expectancy, advanced complications/ comorbidities
American Geriatric Society[7]	7% to 7.5%†	Healthy with few comorbidities and good functional status
	7.5% to 8%†	General target for older adults
	8% to 9%‡	Multiple comorbidities, poor health, limited life expectancy
International Diabetes Federation Global Guideline for Managing Older People with T2D[8]	7.0% to 7.5%*	Functionally independent: no ADL impairment and no or minimal caregiver support
	7.0% to 8.0%*	Functionally dependent: ADL impairment, increased likelihood of requiring additional care
	<8.5%*	Functionally dependent and frail, or with dementia

Abbreviations: ADL, activities of daily living; HbA1c, glycated hemoglobin; T2D, type 2 diabetes.
Strength of evidence: †1, strong, based on randomized clinical trial(s); ‡2, strong, based on clinical trial(s) or other analytical studies; *3, weaker, expert consensus.

associated with dangerous sequelae including loss of consciousness, altered mental status, weakness, and CV events, consequences that adversely impact quality of life and lead to increased utilization of health care resources.[10,11] In a retrospective analysis of patients aged 65 years and older, hospitalizations for hypoglycemia were shown to exceed those for hyperglycemia (429,850 vs 302,095, respectively). Further, although rates for hyperglycemia declined by nearly 40% from 1999 to 2011, rates for hypoglycemia increased by 12%.[12] It may be noted that both incremental increases in glucose concentrations, as well as hypoglycemia episodes requiring medical intervention in older patients have been shown to increase the risk for dementia, underlining the importance of maintaining adequate glycemic control.[13,14]

Multiple risk factors may contribute to the development of hypoglycemia in older patients, including cognitive impairment, poor nutrition, polypharmacy, recent hospitalization, and organ dysfunction.[15] The symptoms of hypoglycemia are sometimes less obvious to older patients, possibly in part because of lack of awareness, and some symptoms may be atypical, such as vague neurologic symptoms that may be misinterpreted as neurologic disease.[16,17] Strategies to prevent hypoglycemic episodes include the identification of precipitating and predisposing factors and the development of an effective management program (eg, patient education, judicious selection of antidiabetes treatments).[17]

Psychological and social factors

The prevalence of depression has been estimated to be significantly higher in older patients with T2DM compared with individuals without T2DM (32% vs 16%).[18] Older patients with T2DM and a history of depression have been shown to have significantly higher glycated hemoglobin (HbA1c) than patients without depression.[18] Comorbid depression has also been shown to increase the risk for complications and mortality.[19,20] The American Geriatric Society (AGS) therefore recommends screening for depression during the first 3 months of treatment and promptly initiating antidepressant treatment for patients with new-onset or recurrent depression.[21]

There is a 1.5- to 2.5-fold increased risk of cognitive dysfunction in patients with T2DM versus without T2DM.[22] Comorbid cognitive dysfunction is associated with poor glycemic control, acute and recurrent hypoglycemia, and poor treatment adherence in older adults.[22,23] In patients with cognitive dysfunction and/or living without social support, simpler regimens and specialized education are particularly important because regimens including multiple daily injections or multiple medications may be difficult to follow, leading to an increased risk for complications.[24,25] Research has also suggested that T2DM and associated insulin resistance in the brain may contribute to the progression of Alzheimer's disease, proposed as type 3 diabetes.[26]

Patient self-care is important in diabetes management; however, behavioral changes required to plan for and accomplish daily tasks (eg, meals, glucose and medication monitoring) can be challenging for older adults because of the significant cognitive input needed and the barrier of poor nutritional habits learned over time.[27] For patients, self-care and social support correlates with improved glycemic out-

comes and quality of life and decreased complications.[28,29] For patients with limited functional status, caregivers play an important role. However, caregivers may be ill prepared to assume diabetes care management when a patient's decline in functioning, cognition, or behavior warrants it.[30] There is therefore a need for additional supportive services, particularly for caregivers of patients with diabetes and impaired cognition.[30]

Polypharmacy and drug-drug interactions

Older adults with T2DM are more likely to have multiple conditions that often require medication; therefore, complex regimens and drug-drug interactions (DDIs) are potential concerns to address in the treatment plan.[21,24] Findings from a recent National Health and Nutrition Examination Survey in older adults showed that the median number of prescription medications doubled from 2 to 4 and the proportion of patients taking 5 medications or more tripled from 12.8% to 39% between 1988 and 2010.[31] Studies have confirmed a correlation between the number of drugs prescribed and the occurrence of DDIs and adverse drug reactions.[32,33] In a study of 630,743 older patients who were dispensed 6 drugs on average, the prevalence of clinically relevant DDIs was 26% and the prevalence of potentially serious DDIs was 5%.[33]

TREATMENT SELECTION IN OLDER PATIENTS WITH T2DM

Metformin, sulfonylureas (SUs), thiazolidinediones (TZDs), and insulin are traditional antidiabetes agents with well-known therapeutic profiles.[4] However, there are some special considerations in including them in treatment plans for older patients. Metformin is the established first-line pharmacologic treatment and is associated with an HbA1c lowering effect of 1.4%, a low risk for hypoglycemia, and a neutral or beneficial effect on weight.[4,34] Metformin is also associated with a reduction in all-cause mortality in individuals with T2DM.[35,36] However, metformin is contraindicated in patients with renal disease or dysfunction, which may limit use (**TABLE 2**), particularly in older patients, in whom a high prevalence of comorbid renal impairment has been observed.[34,37] When used with any other medication that competes for renal excretion or deteriorates renal function, concentrations of metformin may increase, which may alter the pharmacologic response or lead to adverse events.[38]

Individually, SUs and TZDs are associated with a robust effect on HbA1c (~1.0% to 1.25%).[39] However, SUs increase the risk for hypoglycemia, which is critical to avoid in older patients with T2DM.[4,8] The AGS particularly cautions against glyburide because it increases the risk for severe prolonged hypoglycemia in older adults.[40] Most SUs are primarily metabolized by the cytochrome P (CYP) 450 2C9 isoenzyme, and any concomitant drug that affects CYP450 2C9 may alter SU drug concentrations in circulation, and thus affect the pharmacologic response and risk for adverse events (ie, hypoglycemia).[38,41] Because TZDs may be associated with edema and heart failure (HF), the American Diabetes Association recommends that TZDs be used very cautiously in older patients with, or at risk for, congestive HF.[4] Potential associations between TZD therapy and bone-related adverse events also warrant careful use (**TABLE 2**).[42]

For older patients in whom oral antidiabetes medications cannot be used, the International Diabetes Federation (IDF) suggests long-acting basal insulin as an option.[8] Prandial formulations, when used in a complex treatment regimen, may be associated with an increased risk for errors in older patients.[8] Because older patients with T2DM already have a greater risk for hypoglycemia and hypoglycemia unawareness, an individualized hypoglycemia management plan (including education on blood glucose monitoring) is essential.[8,43]

Incretin-based therapies

The pathophysiology of T2DM involves insulin resistance in the muscle and liver and β-cell dysfunction, as well as various other defects.[44] The incretin effect, a marked increase in insulin secretion following oral ingestion of nutrients, is primarily attributed to the actions of the gut-derived hormones, glucose-dependent insulinotropic peptide (GIP) and GLP-1, which stimulate insulin release in a strictly glucose-dependent fashion.[45] GLP-1 is further associated with glucose-dependent suppression of pancreatic α-cell glucagon secretion, slowing of gastric emptying, and decreased appetite and food ingestion.[46] However, GIP and GLP-1 hormones are rapidly inactivated via the DPP-4 enzyme.[46] The development of incretin-based drugs has therefore focused on increasing circulating levels of endogenous incretin hormones by inhibiting their degradation and thus increasing activity (DPP-4 inhibitors), or by mimicking the action of the endogenous hormone at the GLP-1 receptor with degradation-resistant agonists (GLP-1 RAs).[46]

DPP-4 inhibitors

Several studies of DPP-4 inhibitors in older patients as monotherapy or add-on to existing metformin, SU, TZD, or insulin therapy have been conducted.[37,47-60] Six of these studies enrolled older patients only,[37,48,54,57-59] and the remaining 9 studies analyzed subgroup data for patients ≥65 years or ≥75 years of age versus younger patients.[47,49-53,55,56,60] Collective study findings showed that DPP-4 inhibitors alone or

TABLE 2 **Overview of clinical effects and treatment considerations for older patients**

Class	General clinical effects[4]	Considerations for older patients	Considerations for patients with renal impairment
Biguanides	• High efficacy • Low risk for hypoglycemia • Neutral/beneficial effect on weight	• Potential DDIs with concomitant medications that are renally excreted or impact renal function[38]	• Contraindicated in patients with renal disease/dysfunction[34]
SU	• High efficacy • Moderate risk for hypoglycemia • Weight gain	• Increased risk for hypoglycemia; increased risk for severe prolonged hypoglycemia with GLY[4,40] • Potential DDIs with concomitant medications metabolized by CYP450 2C9 isoenzyme[38]	• Increased risk for prolonged hypoglycemia[91]
TZD	• High efficacy • Low risk for hypoglycemia • Weight gain	• Risk of edema and HF[4] • Cautious use in older patients with or at risk for congestive HF[4] • Potential association with bone-related AEs[42]	• No dose adjustment needed[92,93]
DPP-4 inhibitor	• Intermediate efficacy • Low risk for hypoglycemia • Neutral effect on weight	• Cautious use, or no use at all, in patients with preexisting HF[5]	• No dose adjustment needed in mild RI[94-97] • Dose adjustment required for ALO, SAXA, and SITA in moderate-to-severe RI or ESRD*[94-96]
GLP-1 RAs	• High efficacy • Low risk for hypoglycemia • Beneficial effect on weight	• Injectable administration may be difficult for some older patients[8] • QW formulations (ALB, DUL, and EXEN QW) may help simplify regimens[98-100] • No dose titration required with EXEN QW[100] • GI side effects and weight loss may be problematic for older patients who are frail or underweight[8]	• Careful use with EXEN BID or QW in elderly patients because of likelihood of decreased renal function[100,101] • EXEN BID or QW should be used with caution in moderate RI, not used in severe RI or ESRD, and used with caution in renal transplant recipients[100,101] • Cautious use initiating/escalating ALB, DUL, LIR in RI to minimize AEs (eg, dehydration) that may worsen renal function[98,99,102]
SGLT2 inhibitor	• Intermediate efficacy • Effective at all stages of T2DM • Low risk for hypoglycemia • Beneficial effect on weight	• Hypovolemia must be corrected before initiating treatment, because of potential for treatment-related intravascular volume depletion[103-105] • Hypovolemia, postural hypotension, and weight loss may limit use[8]	• Reduced efficacy and increased AEs with worsened renal function[106,107] • Renal MOA excludes patients with severe RI, ESRD, and dialysis[103-105] • DAPA should not be used in patients with eGFR <60 mL/min/1.73 m^2 [103] • CANA and EMPA should not be used in patients with eGFR <45 mL/min/1.73 m^2 [104,105]

Abbreviations: AE, adverse event; ALB, albiglutide; ALO, alogliptin; BID, twice daily; CANA, canagliflozin; CYP, cytochrome P; DAPA, dapagliflozin; DDI, drug-drug interaction; DPP, dipeptidyl peptidase; DUL, dulaglutide; EMPA, empagliflozin; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; EXEN, exenatide; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide 1 receptor agonist; GLY, glyburide; HF, heart failure; LINA, linagliptin; LIR, liraglutide; MOA, mechanism of action; MET, metformin; QW, once weekly; RI, renal impairment; SAXA, saxagliptin; SGLT, sodium-glucose cotransporter; SITA, sitagliptin; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.

*No dose adjustment needed with LINA for patients with varying degrees of renal impairment.[97]

in combination with other antidiabetes drugs significantly reduced HbA1c versus placebo/active comparator (mean change: –0.1% to –1.1% vs 0.2% to –0.8%, respectively). In addition, the rates of hypoglycemia were low with DPP-4 inhibitors vs placebo/active comparator as monotherapy or add-on to metformin or TZD (incidence: 0 to 5.8% vs 0 to 34.8%, respectively). Rates of hypoglycemia were somewhat higher but similar to placebo in studies investigating DPP-4

inhibitors as add-on therapy to an SU and/or insulin (incidence: 21.4% to 24.1% vs 16.5% to 25.7%, respectively).[37,58] Interestingly, the results of a meta-analysis conducted to explore determinants of response to DPP-4 inhibitors showed that older age was associated with improved efficacy.[61] DPP-4 inhibitors have been observed to be weight neutral, thus offering additional advantages for the management of T2DM compared with therapies associated with weight gain (eg, TZD, SU, insulin).[4,46]

Cardiovascular disease is the major cause of morbidity and mortality in T2DM, with age as a strong predictor of CV complications.[4] In fact, the IDF considers all patients with diabetes older than 60 years of age at high risk for CV disease.[8] The US Food and Drug Administration now requires new antidiabetes medications to show no unacceptable increase in CV risk.[62]

To date, 2 randomized CV outcomes trials for linagliptin are ongoing,[63,64] and 3 CV outcomes trials for saxagliptin (SAVOR), alogliptin (EXAMINE), and sitagliptin (TECOS) have reported findings.[65-67] Although differences in patient populations and study designs do not allow direct comparisons among the studies, collective findings indicate that DPP-4 inhibitors as add-on to standard of care do not increase the risk for major CV events, as defined by the primary composite end point of CV death, nonfatal myocardial infarction (MI) or nonfatal stroke (SAVOR, EXAMINE) or CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina (TECOS).[65-67]

Subgroup analyses of the primary composite end point in each of the trials showed no significant interaction between patients aged younger than 65 years or those 65 years and older.[68-70] Additional findings from SAVOR and EXAMINE suggest that certain patients may have an increased risk for hospitalization for HF,[65,71] although this was not observed in TECOS.[67] Additional data from the 2 ongoing CV outcomes trials for linagliptin should provide further insight into this potential risk.[63,64] However, until additional outcomes are known, treatment guidelines advise using DPP-4 inhibitors cautiously, or not at all, in patients with preexisting HF.[5]

GLP-1 RAs

There are limited studies for GLP-1 RAs reporting data specifically for older patients. Of the available data, findings have shown exenatide and liraglutide administered as monotherapy or as add-on to existing antidiabetes therapy to significantly reduce HbA1c compared with placebo or active comparator (mean decrease: –0.5% to –1.4% vs –0.2% to –0.5%) and weight in patients older than 65 years of age, with changes generally comparable to those of younger patients.[72-74] In addition, no cases of major hypoglycemia were reported in older patients, and rates of hypoglycemia were similar in patients aged 65 years and older compared with those younger than 65 years (incidence: 4.3% to 15.2% vs 6.4% to 13.2%) and similar to placebo (9.1%).[73,74] The occurrence of minor hypoglycemia was more frequent in patients in both age groups who were also taking an SU compared with no SU (incidence: 12.0% to 12.7% vs 2.0% to 4.2%).[73]

Most of the long-term randomized CV outcomes trials for GLP-1 RAs are ongoing, and most include patients with preexisting CV disease or CV risk factors.[75] Preliminary findings from the lixisenatide study (ELIXA) in patients with a recent acute coronary syndrome episode have been reported. After follow-up of more than 2 years, patients (N=6068) had no increased risk for CV death, MI, stroke, unstable angina, or HF with lixisenatide compared with placebo.[76] Although additional data are needed to better establish the CV risk associated with GLP-1 RA therapy, outcomes from cohort studies also indicate no increased risk for CV events with treatment, and a possible reduction in some CV events.[77] Results from a meta-analysis of GLP-1 RAs including 20 studies of albiglutide, exenatide twice daily, exenatide once weekly, and liraglutide have also shown no increased risk for major CV events with treatment vs placebo or active controls.[78]

SGLT2 inhibitors

In healthy, normal glucose-tolerant individuals, nearly all filtered glucose is reabsorbed by the proximal renal tubule for recirculation.[79] The SGLT2 protein, a high capacity, low-affinity transporter, is responsible for the majority (90%) of renal glucose reabsorption.[79] In T2DM, the capacity for renal glucose reabsorption is increased, leading to continued glucose reabsorption despite hyperglycemia. The inhibition of SGLT2 therefore increases glucose excretion in the urine, independently of insulin secretion or action, and thereby reduces glucose reabsorption and facilitates caloric loss.[79]

Published clinical trial data have shown that canagliflozin monotherapy and combination therapy effectively lower HbA1c (placebo-corrected mean decrease: –0.6% to –0.8%) and reduce body weight, without increasing the overall risk for hypoglycemia (incidence: 4.0% to 36.0% vs 3.6% to 28.7% with placebo).[80,81] Where assessed, the efficacy and tolerability of canagliflozin in older patients was similar to that of a younger cohort.[80] Pooled safety data have also shown dapagliflozin to have an adverse event profile in older patients consistent with that of SGLT2 inhibitors, and a rate of hypoglycemia similar to that of placebo (incidence: 20.2% vs 17.7%).[82] In older patients with preexisting CV disease and hypertension, dapagliflozin added to existing therapy compared with placebo has also been shown to significantly

reduce HbA1c (mean change: –0.3% to –0.4% vs 0.1% to 0.2%) and body weight, with no increased risk for hypoglycemia (incidence: 21.0% to 25.2% vs 16.4% to 26.2%).[83,84]

Findings from the CV outcomes trial for empagliflozin were recently published, and randomized placebo-controlled CV outcomes trials for canagliflozin and dapagliflozin are underway.[85-87] In the empagliflozin study (EMPA-REG OUTCOME), 7020 patients with established CV disease were randomized and treated with empagliflozin or placebo as add-on to standard of care. The mean baseline age was 63 years. A significantly lower rate of major CV events, death from CV causes, death from any cause, and hospitalization for HF was reported in the empagliflozin vs placebo group. Subgroup analyses showed consistent benefit with empagliflozin over placebo in patients 65 years of age and older in the risk of major CV events and death from CV causes.[87,88] To date, CANVAS, the CV outcomes trial for canagliflozin, has randomized 4330 patients with an increased CV risk and mean baseline age of 62 years.[85] Although baseline characteristics for the dapagliflozin study (DECLARE-TIMI58) have yet to be published, inclusion criteria requiring patients to be at least 40 years of age with a high risk for CV events indicates a similar population.[86]

SUMMARY

The treatment of older patients with T2DM is often not as straightforward as that of their younger counterparts. The heterogeneous nature of the older population requires that treatment goals be individualized with consideration of the potential risks and benefits. Intensive treatment with certain antihyperglycemic medications may pose undue risks in patients who are frail, have a short life expectancy, or have CV disease. Guidelines generally advocate for less stringent HbA1c goals in older patients and focus on minimizing the risk for complications.[4-8] Collaboration with family and caregivers is also emphasized.[7] The avoidance of hypoglycemia should be a primary goal for older patients, and antidiabetes medications that increase the risk for hypoglycemia (eg, SUs, insulin) should be used with caution.[4,7,8,40] The impaired response to hypoglycemia in older adults also makes the use of treatments with glucose-dependent or insulin-independent mechanisms that have a low propensity to cause hypoglycemia more favorable.

Available data for DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors suggest that these agents may be well suited for many older patients with T2DM, given demonstrated efficacy, neutral or beneficial effects on weight, and low risk for hypoglycemia. In general, GLP-1 RAs have a more robust effect on glycemic lowering than DPP-4 inhibitors or SGLT2 inhibitors.[4] The mechanisms of DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors complement those of most other antidiabetes agents, including insulin, and combination regimens including these agents should therefore provide effective glycemic control.

Some precautions for use in the general T2DM population also apply to older patients, and these must be considered in the treatment decision (**TABLE 2**). Dosing and treatment considerations in older patients are mainly related to declining renal function and use of concomitant medications. Renal impairment is common in older patients with T2DM.[37]

Although DPP-4 inhibitors have been shown to be efficacious and well tolerated in patients with moderate-to-severe renal impairment, dosing adjustments may be required.[6,89,90] Specific precautions for patients with differing degrees of renal impairment are also noted for GLP-1 RAs and SGLT2 inhibitors. In patients with preexisting HF, current guidance recommends that DPP-4 inhibitors be used cautiously, or not at all, until additional trial findings are known.[5] In addition, because GLP-1 RAs[4] are associated with weight loss, they are not recommended for use in frail or underweight older patients.[8] Similarly, because of associated weight loss and diuretic effects, SGLT2 inhibitors should be used carefully in the frail elderly.[4,5] For older patients with T2DM without these specific concerns, the individual therapeutic profiles of DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors indicate each is a beneficial treatment option that improves glycemic control without increasing the risk for hypoglycemia. ●

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Nonsteroidal Anti-inflammatory Drugs and Cardiovascular Risk: Where Are We Today?

Gary Ruoff, MD

Since discovery of an increased risk of cardiovascular (CV) events with nonsteroidal anti-inflammatory drugs (NSAIDs) a decade ago, additional analyses have been conducted to provide further insight and assess if differences exist among the NSAIDs regarding CV risk. Interpretation of these analyses led the US Food and Drug Administration (FDA) in July 2015 to require further labeling changes for all prescription and nonprescription NSAIDs. Despite differences in how the analyses were conducted, the results suggest that differences in CV risk may exist among the NSAIDs. This article provides an overview of key findings related to the CV risk of NSAIDs and their implications for management in the primary care setting.

HISTORICAL OVERVIEW

In 2000, the results of the VIGOR (Vioxx gastrointestinal outcomes research) study were the first hint that CV events might be more common with selective cyclooxygenase (COX-2) inhibitors (coxibs) than with nonselective or "traditional" NSAIDs (tNSAIDs), in this case, naproxen.[1] By the time the results of the APPROVe (adenomatous polyp prevention on Vioxx) study had been published in 2005, rofecoxib had been voluntarily withdrawn from the market.[2] The APPROVe study showed a 1.92 relative risk of confirmed thrombotic events, over more than 6000 patient-years of follow-up in patients treated with rofecoxib compared with placebo (95% confidence interval [CI], 1.19-3.11; *P*=.008). The relative risk of nonadjudicated investigator-reported congestive heart failure, pulmonary edema, or cardiac failure with rofecoxib was 4.61 (95% CI, 1.50-18.83).[2]

The CV risks associated with coxibs and tNSAIDs were discussed by a joint meeting of 2 FDA advisory committees in February 2005.[3] The findings of this meeting led to the withdrawal of valdecoxib from the market and labeling changes for prescription and nonprescription NSAIDs regarding increased risk of CV events and gastrointestinal (GI) bleeding.[4] Celecoxib, the prototype coxib, was allowed to remain on the market in the United States.

Since 2005, additional events related to the safety of NSAIDs have occurred. The PRECISION study was initiated to compare the CV risks of celecoxib (100-200 mg twice daily), ibuprofen (600-800 mg 3 times daily), and naproxen (375-500 mg twice daily) in patients with osteoarthritis or rheumatoid arthritis who have established or risk factors for CV disease.[5] PRECISION has enrolled more than 24,000 patients and is scheduled for completion late in 2016. Subsequent to the initiation of PRECISION, 2 meta-analyses (discussed below) suggested differences might exist among NSAIDs regarding CV risk.[6,7] One of these, the Coxib and Traditional NSAID Trialists' (CNT) Collaboration concluded: "The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs. Although NSAIDs increase vascular and GI risks, the size of these risks can be predicted, which could help guide clinical decision making."[7]

In February 2014, the FDA convened a joint meeting of the same 2 advisory committees to review the CNT meta-analysis and other information since the 2005 meeting.[8] Based on this meeting and its own analysis, the FDA reached several conclusions regarding the CV risks of NSAIDs (**TABLE**).[9] As a consequence, the FDA is strengthening the labeling requirements of all prescription NSAIDs to indicate that their use is associated with an increased risk of a heart attack or stroke. This information is already included in the labeling of nonprescription NSAIDs.

MECHANISTIC BASIS FOR A CARDIOVASCULAR HAZARD

NSAIDs inhibit endothelial cyclooxygenase, thus inhibiting

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DISCLOSURES

Dr. Ruoff discloses that he is on the speakers' bureaus for Takeda Pharmaceuticals U.S.A., Inc.; and the advisory board for AstraZeneca and Blue Cross Blue Shield Pharmacy Committee.

ACKNOWLEDGMENT

Editorial support was provided by Gregory Scott, PharmD, RPh; Dana Randall, MS, PharmD, RPh.

SUPPORT

This article is sponsored and developed by Primary Care Education Consortium.

TABLE US FDA conclusions after February 2014 advisory committee meeting on cardiovascular safety of NSAIDs[9]

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke after NSAID use than patients without these risk factors because they have a higher risk at baseline.
- Patients treated with NSAIDs after a first heart attack were more likely to die during the first year after the heart attack compared with patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use.

NSAID, nonsteroidal anti-inflammatory drug.

the conversion of arachidonic acid to prostaglandin H_2 and subsequent production of bioactive prostanoids, including thromboxane A_2 (TxA_2) and prostacyclin (PGI_2).[10] NSAIDs selective for the COX-2 isozyme result in greater inhibition of prostacyclin synthesis and a lower risk of upper GI bleeding compared with tNSAIDs.[10] Suppression of vascular prostacyclin, which normally restrains thrombogenesis by reducing platelet activation and aggregation, does not cause spontaneous thrombosis, but rather augments the response to thrombogenic stimuli in vivo in a dose-dependent manner.[11-13]

Both COX-1 and COX-2 are irreversibly inhibited by aspirin, but it is the inhibition of COX-1 that confers its antiplatelet effects, resulting in profound and persistent inhibition of TxA_2 production and TxA_2-dependent platelet activation. NSAIDs may variably interfere with the antiplatelet action of aspirin by forming hydrogen bonds with amino acids of the COX-1 hydrophobic channel.[14] Because coxibs and most tNSAIDs, except naproxen, cause only transient and modest inhibition of COX-1 insufficient to inhibit atherothrombosis, overall antiplatelet activity may be compromised when an NSAID is combined with aspirin.[10]

EVIDENCE FROM META-ANALYSES

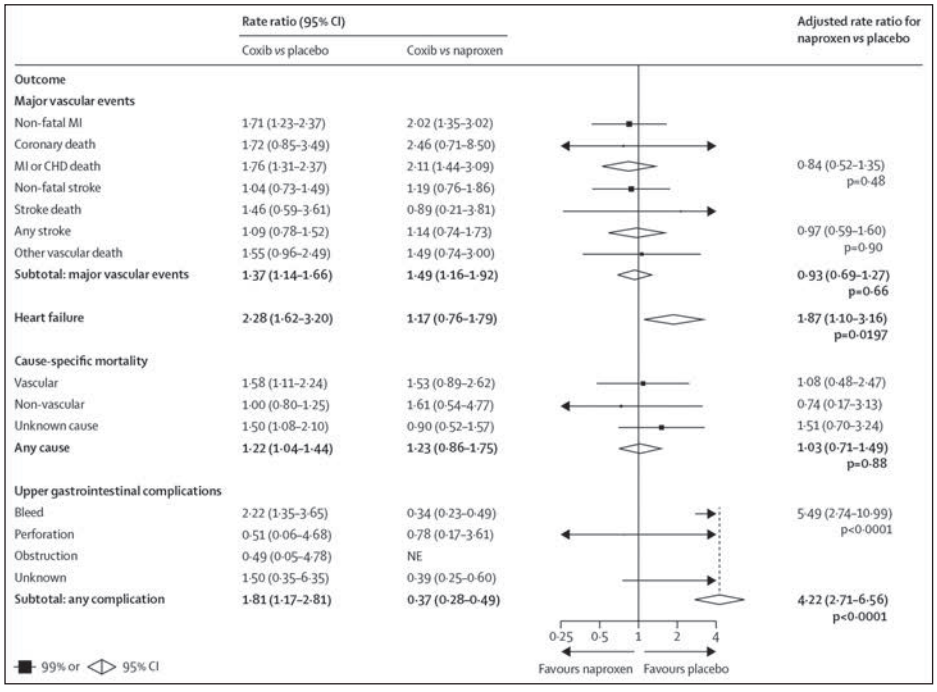
The CNT Collaboration was the first meta-analysis to estimate CV and GI treatment effects by comparing the results of coxib versus placebo trials with those of coxib versus tNSAID trials.[7] In addition, most of the 639 trials included in the CNT analysis provided individual participant data (mean age, 61 years; two-thirds female; ~80% white). The CNT meta-analysis and a previous meta-analysis of 28 observational studies by Castellsague showed a higher risk of upper GI bleeding with tNSAIDs compared with coxibs. The Castellsague meta-analysis showed that the pooled relative risk was <2 for celecoxib and ibuprofen; 2 through <4 for sulindac, diclofenac, meloxicam, and ketoprofen; 4 through <5 for naproxen, indomethacin, and diflunisal; and >5 for piroxicam and ketorolac.[15] The rate ratios of upper GI complications (primarily bleeding) in the CNT analysis were: coxibs 1.81; diclofenac 1.89; ibuprofen 3.97; and naproxen 4.22.[7]

CARDIOVASCULAR RISK

The main CV outcomes in the CNT meta-analysis were major vascular events (MVE; nonfatal myocardial infarction [MI], nonfatal stroke, or vascular death), major coronary events (nonfatal MI or coronary death), stroke, heart failure, and vascular mortality.[7] The estimation of CV risk was based on trials of celecoxib and 3 coxibs not available in the United States (rofecoxib, etoricoxib, and lumiracoxib) and 3 high-dose tNSAID regimens (diclofenac 150 mg/d, ibuprofen 2400 mg/d, and naproxen 1000 mg/d).[7] The risk of MVE was increased by approximately one-third in patients taking coxibs (rate ratio, 1.37; 95% CI, 1.14-1.66; *P*=.0009) or diclofenac (1.41; 95% CI, 1.12-1.78; *P*=.0036) compared with placebo **(FIGURE)**.[7] The MVE risk was 1.36 (99% CI, 0.91-2.02) for celecoxib and 1.38 (99% CI, 0.99-1.94) for rofecoxib. The increased MVE risk for patients taking coxibs was primarily due to a higher risk of major coronary events (1.76; 95% CI, 1.31-2.37; *P*=.0001). In patients taking ibuprofen, the risk of major coronary events was also significantly increased (2.22; 95% CI, 1.10-4.48; *P*=.0253) but the risk of MVE was not (1.44; 95% CI, 0.89-2.33; *P*=.14). By comparison, high-dose naproxen was not associated with an excess risk of either MVE or major coronary events (0.93; 95% CI, 0.69-1.27; *P*=.66).

Compared with placebo, the risk of stroke was not increased by any NSAID in the CNT analysis.[7] The risk of hospitalization secondary to heart failure was doubled by all NSAIDs studied: 2.49 (95% CI, 1.19-5.20; *P*=.0155) for ibuprofen, 2.28 (95% CI, 1.62-3.20; *P*<.0001) for coxibs, 1.87 (95% CI, 1.10-3.16; *P*=.0197) for naproxen **(FIGURE)**, and 1.85 (95% CI, 1.17-2.94; *P*=.0088) for diclofenac. Coxibs and diclofenac significantly increased the risk of vascular death (1.58; 99% CI, 1.00-2.49; *P*=.0103), whereas ibuprofen was

FIGURE Effects of coxibs and naproxen on major cardiovascular events and heart failure[7]



Adjusted rate ratios for comparisons of a tNSAID with placebo were calculated indirectly from ratios of rate ratios for coxibs versus placebo and coxibs versus tNSAIDs.

Actual numbers for participants are presented, together with the corresponding mean yearly event rate in parentheses. Participants can contribute only once to the total of major vascular events (myocardial infarction, stroke, or vascular death). Rate ratios (RRs) for all outcomes are indicated by squares and their 99% confidence intervals (CIs) by horizontal lines. Subtotals and their 95% CIs are represented by diamonds. Squares with horizontal line or diamonds completely to the left of the solid vertical line at 1 indicate statistically significant benefit with the specific NSAID.

CHD, coronary heart disease, MI, myocardial infarction; tNSAID, "traditional" NSAID.

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associated with a nonsignificant increase (1.90; 99% CI, 0.56-6.41; *P*=.17) and naproxen with no increase (1.08; 99% CI, 0.48-2.47; *P*=.80).

Overall, the CNT meta-analysis indicated that vascular risks associated with different coxib regimens appeared to be similar and that vascular risks associated with high-dose diclofenac regimens parallel those of typical coxib regimens.[7] High-dose ibuprofen was also associated with a significantly increased risk of major coronary events; however, this result should be interpreted cautiously given the smaller number of relevant vascular events in trials comparing coxibs and ibuprofen. High-dose naproxen did not increase the risk of MVE, major coronary events, or death, likely due to sufficiently prolonged and intense platelet inhibition that may attenuate any adverse vascular effects. It is uncertain if lower, nonprescription doses of naproxen would have a similar effect.

Results of the CNT meta-analysis of randomized controlled trials provided generally similar findings as an earlier meta-analysis by McGettigan and Henry of population-based, controlled observational studies of individual NSAIDs used at typical doses in community settings.[6] For example, for tNSAIDs, the estimated relative risks for major CV events were high with diclofenac (1.40; 95% CI, 1.27-1.55) and low with ibuprofen (1.18; 95% CI, 1.11-1.25) and naproxen (1.09; 95% CI, 1.02-1.16) (all *P*<.0001).[6] However, the McGettigan-Henry meta-analysis also revealed a large difference in relative risk between celecoxib (1.17; 95% CI, 1.08-1.27; *P*<.0001) and rofecoxib (1.45; 95% CI, 1.33-1.59; *P*<.0001),[6] whereas the CNT analysis reported a risk of 1.36 for celecoxib and 1.38 for rofecoxib.[7]

A recent report of results from the Standard Care vs Celecoxib Outcome Trial (SCOT) at the 2015 European Society of Cardiology meeting provides some reassurance regarding NSAID safety.[16] The SCOT trial randomized 7297 patients with arthritis at low risk of a CV event to celecoxib or "standard" nonspecific NSAIDs. After 3 years of follow-up, the number of CV endpoints (CV death or hospitalization for biomarker-positive acute coronary syndromes) was very low and similar in both groups (celecoxib 1.8% vs NSAIDs 2.2%: hazard ratio=1.12; 95% CI, 0.81-1.55; *P*=.50). Ulcer-related upper GI complications were also uncommon, with no difference between groups.

IMPLICATIONS FOR PATIENT MANAGEMENT

Insights into the CV effects of coxibs and tNSAIDs continue to evolve, but differing methodologies among meta-analyses have sometimes led to conflicting results and ongoing controversy. The CNT meta-analysis of randomized controlled trials[7] avoids limitations associated with observational studies, such as selection and other biases, while meta-analysis of observational studies (such as the McGettigan-Henry analysis) overcome potential limitations associated with

randomized controlled trials, including small sample sizes, limited number of events, narrowly defined populations, a limited number of individual NSAIDs and doses, and short duration of follow-up.[6] These and other differences in the design of meta-analyses, such as the types of studies analyzed, the statistical methods used, and patient populations, can contribute to different conclusions. For example, in the CNT trial, CV risks associated with NSAIDs were compared with placebo, whereas in the McGettigan-Henry analysis, risks were compared with no treatment. Also, the risks in the McGettigan-Henry analysis were based on data from patients with rheumatoid arthritis who received approved coxib doses, but risks in the CNT trial were not based on data from patients with rheumatoid arthritis. Moreover, the effect of celecoxib was dose-dependent and driven primarily by CV effects observed at a dose of 800 mg/d.[7]

The indirect comparisons of tNSAIDs with placebo to assess comparative CV risk in the CNT meta-analysis should be interpreted cautiously. The CNT meta-analysis quantified the CV risk of coxibs vs placebo by comparing a coxib directly with placebo. By contrast, the CV risk of tNSAIDs vs placebo was quantified indirectly by first comparing a tNSAID with a coxib, then that coxib with placebo. Indirect comparisons include a number of limitations such as the coxib compared with placebo is not necessarily the coxib compared with a tNSAID, the 2 coxibs in the analysis were not used at comparable doses or in patients at similar risk, and certain coxibs were preferentially compared with certain tNSAIDs.

Despite these limitations, it is reasonable to conclude that coxibs and most tNSAIDs such as diclofenac are associated with an increased risk of a MVE (nonfatal MI, nonfatal stroke, vascular death) but not stroke. Naproxen appears to be an exception as it was not associated with an excess risk of MVE, major coronary event, or stroke. Ibuprofen may also be associated with a low risk of MVE; however, findings from the CNT and McGettigan-Henry meta-analyses conflict.

It is important to realize that the results of the CNT and McGettigan-Henry meta-analyses are provided in terms of relative risk. If the results are considered from an absolute risk perspective, the CNT analysis showed that a coxib or diclofenac resulted in approximately 3 additional CV events per 1000 participants per year. The excess risk of other tNSAIDs was less.[7] Albeit generally more serious, it is clear that the absolute risk of a CV event is much lower than an upper GI bleed. Moreover, the CNT analysis found that one CV event per 1000 participants per year was fatal compared with 2% of upper GI complications.

While awaiting the results of the PRECISION trial, the CNT and McGettigan-Henry meta-analyses and FDA actions have important implications for primary care providers. First, the FDA has not recommended that NSAIDs are to be avoided, which reflects the low absolute risk of a CV event. The FDA does recommend that NSAIDs be used at the lowest effective dose and for the shortest time possible with appropriate monitoring. Patient selection is important, especially for patients with established heart disease or risk factors, as well as risk factors for a GI bleed. Although the FDA did not differentiate among the NSAIDs regarding CV risk, both the CNT and McGettigan-Henry analyses indicated differences among the NSAIDs, with naproxen, and possibly ibuprofen, associated with the lowest CV risk. However, the risk of an upper GI bleed with naproxen is higher than several other tNSAIDs. Although infrequently fatal and potentially managed with a proton pump inhibitor, the possibility of an upper GI bleed with NSAID therapy should be discussed with patients. This discussion should also include the benefits and risks of alternative medications. ●

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Individualizing Inhaled Medications for Asthma and Allergic Rhinitis

Leonard Fromer, MD, FAAFP

INTRODUCTION

Allergic rhinitis (AR) is described as a chronic inflammatory disease of the upper airways characterized by nasal congestion, rhinorrhea, sneezing, and nasal itching. Asthma is characterized by an eosinophilic inflammatory process present throughout the large and small peripheral airways and also by reversible airflow obstruction.[1] Evidence, in the form of links between AR and asthma at the anatomic, physiologic, pathologic, and therapeutic levels, supports the concept of a "unified airway"—the upper and lower airways function as a single unit and that disease processes may be interrelated.[2] Recent surveys indicate that approximately 78% of patients with asthma have AR and 38% of patients with AR have asthma.[3] Several studies have shown that treatment of AR in patients with asthma can improve asthma control and reduce health care costs.[4,5]

ROLE OF INHALED MEDICATIONS IN THERAPY

The pathophysiologic mechanisms involved in asthma and AR lend themselves to management with orally inhaled (asthma) or intranasal (AR) medications. For asthma, inhaled short- and long-acting beta$_2$ agonists and corticosteroids are key treatment options, while for AR, intranasal corticosteroids and antihistamines are primary therapeutic options.[6-8] Current asthma treatment guidelines classify orally inhaled corticosteroids (ICS) as low-, mid-, and high-dose based on estimated clinical comparability.[6] Among available intranasal corticosteroids, the overall clinical response appears comparable, and none of the intranasal corticosteroids is generally associated with clinically significant systemic side effects in recommended doses.[8]

Over the past decade and more, numerous beta$_2$ agonists and corticosteroid molecules, as well as a wide variety of inhaler devices, have become available. A systematic review suggests that the various inhaler devices available for asthma can work equally well in various clinical settings with patients who can use these devices properly.[9] A consortium of experts has identified over 50 critical inhaler handling errors associated with various inhaler devices that are likely to significantly impair delivery of adequate medication.[10] Of equal concern is that studies have shown that only 15% to 69% of health care professionals can demonstrate correct inhaler use.[10]

The challenge for health care providers is to select the inhaler best suited for an individual patient and teach proper administration technique since these directly impact adherence. In addition, correct administration technique is critical since it is the primary barrier to effectiveness of inhaled medication and achieving the optimal therapeutic response from the drug.[11-14] Clinical consequences of poor inhaler technique include: instability of asthma and increased emergency room visits, hospitalization, and oral medication prescriptions.[13,14]

Assessing potential barriers to effective use of inhaled medications is important at every visit. Patients should demonstrate inhaler technique and be questioned about experiences with unpleasant local side effects such as a bad taste or oral thrush (a potential risk with oral corticosteroid inhalers).[10] Factors that may affect patient satisfaction with and adherence to intranasal medication include nose and throat irritation, medication dripping down the throat, scent, or "wet vs dry" spray.[15] If a barrier is identified, verifying correct inhaler administration or selecting a different inhaler are options.

This article reviews the wide variety of inhaler formulations (oral and intranasal) and devices. Suggestions for individualizing inhaler selection are also provided.

INHALER DEVICES AND FORMULATIONS

In addition to intranasal and orally inhaled formulations, inhalers are available as aqueous or dry powder formulations and as metered-dose or breath-actuated devices.

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DISCLOSURES

Dr. Fromer discloses that he is on the speakers' bureau for Meda Pharmaceuticals Inc. and Thermo Fischer Scientific, Inc.

ACKNOWLEDGMENT

Editorial support was provided by Angela Cimmino, PharmD; Gregory Scott, PharmD, RPh.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from Teva Pharmaceuticals, USA, Inc.

TABLE 1 Intranasal corticosteroids

Aqueous	Nonaqueous
Beclomethasone (Beconase AQ, Vancenase AQ)	Beclomethasone (QNASL Nasal Aerosol)
Budesonide (Rhinocort Aqua)	Ciclesonide (Zetonna Nasal Aerosol)
Ciclesonide (Omnaris)	
Flunisolide (Nasalide, Nasarel)	
Fluticasone furoate (Veramyst)	
Fluticasone propionate (Flonase)	
Mometasone (Nasonex)	
Triamcinolone (Nasacort AQ)	
Fluticasone propionate/azelastine[a] (Dymista)	

[a]Combination corticosteroid and antihistamine.
Source: US Food and Drug Administration. Drugs@FDA. www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

Nasal inhalers: Aqueous vs aerosol

Most intranasal corticosteroids are available as an aqueous formulation, but hydrofluoroalkane (HFA)-propelled nonaqueous aerosol intranasal corticosteroids have been approved in the last few years (**TABLE 1**).[16] Aqueous products are typically available in a nasal pump dispenser. Proper administration requires the patient to tilt their head back, close the contralateral nostril with a finger, and sniff inward during activation of the spray. Nonaqueous products are delivered through an aerosol device with a metering valve that converts solid or liquid corticosteroid particles into a gaseous suspension using a propellant. The patient closes one nostril with a finger, gently inserts the tip of the nosepiece in the other nostril, and holds the breath while pressing down on the canister to deliver the prescribed number of actuations.[16]

Both formulations appear to have similar efficacy rates.[17] It has been suggested that the HFA formulations may have a preferable sensory profile for some patients in terms of possibly improving some of the bothersome side effects associated with aqueous formulations (such as taste, posterior and anterior runoff, and fragrance), but no study has documented differences in patient adherence by type of formulation.[16]

Oral inhalers: Formulations

Aerosols for inhalation are either solutions, suspensions of solid drug particles in a gas, or dry powder solid particles, which can be generated from devices such as pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers (**TABLE 2**); only pMDIs and DPIs are discussed in this article.[11] The efficiency of drug delivery to the lower respiratory tract varies among inhalers based on the type of device, its internal resistance, formulation of the medication, particle size, velocity of the produced aerosol plume, and ease with which patients can use the device.[11]

Aerodynamic diameter is thought to be the most important particle-related factor influencing the deposition pattern of a drug in the lungs, and optimal particle size range for inhalation seems to be 1.5-5 μm, with most particles >5 μm impacting on the oropharynx, and many particles ≤1 μm being exhaled.[18,19] Most current inhalers generate aerosols with a significant proportion of their particles in the 1 to 5 μm range.[18] Several of the newer products generate smaller 'ultrafine' particles which may provide enhanced control because of their improved delivery to the peripheral small airways; however, it is not yet clear that such targeted therapy improves peripheral inflammation/small airway disease over standard ICS MDIs and DPIs.[20] The products generating "ultrafine" particles have been associated with lower oropharyngeal impaction and similar lung deposition when inhaled with either slow or fast inhalation flow, and when actuation and inhalation were not completely coordinated.[21]

Oral inhalers: pMDI vs DPI

The pMDI is the most widely prescribed inhalation device for drug delivery to the respiratory tract to treat asthma (**TABLE 3**). The canister contains a pressurized suspension or solution of micronized drug particles dispersed in a propellant. A surfactant added to reduce particle agglomeration is also responsible for the characteristic taste of specific inhaler brands.[11] The operation of the pMDI requires pressing the bottom of the canister into the actuator which causes decompression of the formulation within the metering valve, resulting in an explosive generation of aerosol droplets that consist of tiny drug particles contained within a shell of propellant.[11]

A major barrier to effective delivery of medication with a pMDI is the difficulty to coordinate device actuation with inhalation and to maintain a slow rate of inhalation for as long as possible. This is a particular challenge for young children and the elderly.[11,22] To overcome this problem, breath-actuated pMDIs were developed. These devices contain a

TABLE 2 Orally inhaled medications for asthma

Device type/drug class	Generic name	Brand/device name	Comments
pMDIs (traditional)			
Beta$_2$-adrenergic agonists	Albuterol	ProAir HFA; Proventil HFA; Ventolin HFA; Xopenex HFA	SABA
Corticosteroids	Beclomethasone HFA	QVAR	Emits ultra-fine particles
	Ciclesonide	Alvesco	Emits ultra-fine particles
	Flunisolide HFA	Aerospan	
	Fluticasone propionate	Flovent HFA	
	Mometasone furoate	Asmanex HFA	
Combinations	Budesonide/formoterol	Symbicort	corticosteroid/LABA
	Fluticasone propionate/salmeterol	Advair HFA	corticosteroid/LABA
	Mometasone furoate/formoterol	Dulera	corticosteroid/LABA
BA-pMDIs			
Beta$_2$-adrenergic agonists	None in the US		
Corticosteroids	None in the US		
DPIs			
Beta$_2$-adrenergic agonists	Albuterol	ProAir RespiClick	SABA
	Formoterol	Foradil Aerolizer	LABA; low resistance DPI
	Salmeterol	Serevent Diskus	LABA; medium resistance DPI
Corticosteroids	Budesonide	Pulmicort Flexhaler	
	Fluticasone propionate	Flovent Diskus	medium resistance DPI
	Fluticasone furoate	Arnuity Ellipta	
	Mometasone furoate	Asmanex Twisthaler	high resistance DPI
Combinations	Fluticasone furoate/vilanterol	Breo Ellipta	corticosteroid/LABA
	Fluticasone propionate/salmeterol	Advair Diskus	corticosteroid/LABA; medium resistance DPI

Abbreviations: BA-pMDI, breath-activated pMDI; DPI, dry powder inhaler; HFA, hydrofluoroalkane; LABA, long-acting beta$_2$-agonist; pMDI, pressurized metered dose inhaler; SABA, short-acting beta$_2$-agonist.
Source: US Food and Drug Administration. Drugs@FDA. www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

conventional pressurized canister and have a flow-triggered system driven by a spring, which releases the dose during inhalation, so that firing and inhaling are automatically coordinated. Use of a breath-actuated pMDI results in drug deposition in the lungs comparable to a traditional pMDI used with good coordination.[23] Results of a study in 102 elderly but cognitively intact patients indicate that breath-actuated pMDIs were significantly more likely to be used correctly than a traditional pMDI, plus a spacer.[24] Children and adults using a breath-actuated pMDI may have better asthma control than patients using a traditional pMDI.[25] No breath-activated pMDIs are currently available in the United States.

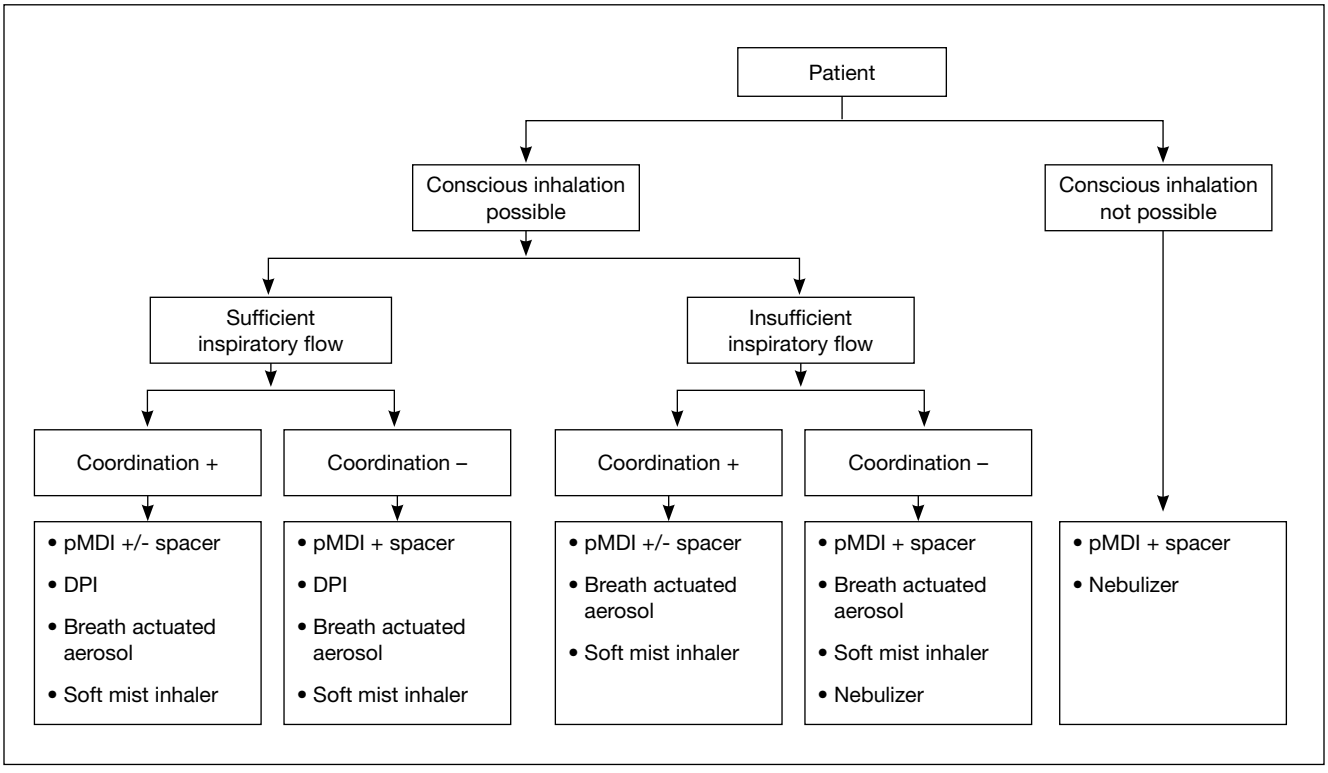
Dry powder inhalers are breath-actuated and require minimum patient coordination between breathing and actuation of the device to deliver powder medications. The dry powder is formulated either as loose agglomerates of micronized drug particles with aerodynamic particle sizes <5 μm or as carrier-based interactive mixtures with micronized drug particles adherent to the surface of large lactose carriers.[11] The powder is aerosolized through the DPI device where drug particles are separated from the carrier or de-agglomerated. Powder formulation and design of DPI devices significantly affect performance. Higher air flow resistance inhalers are typically more effective in dispersing the dry power during inhalation and, therefore, provide greater lung deposition than lower internal resistance inhalers. Clinical experience shows that most patients can use a high-resistance DPI effectively, even during exacerbations.[11,19] Several studies have demonstrated fewer inhalation errors with DPIs compared with pMDIs.[22,26-28]

TABLE 3 Advantages and disadvantages of inhaler devices[18]

Type	Advantages	Disadvantages
HFA-pMDIs (suspension and solution)	• Portable and compact • No contamination risk • High reproducibility between doses	• Coordination of actuation and inhalation needed • Most patients inhale too fast • Low lung deposition and high oropharyngeal deposition • Important to prime before use if new or not used in some time, and to shake before use • Must be kept upright during inhalation • With most devices, the number of doses remaining is difficult to determine; not all pMDIs have dose counters
HFA-pMDIs (extra-fine particles)	• As above for pMDIs • Higher lung deposition and lower oropharyngeal deposition, compared with pMDIs that are used alone • Good for inhaled corticosteroids • Corticosteroid dose should be halved if prescribed for patients previously using other traditional corticosteroid pMDI • Optimal inhalation technique less important than with traditional pMDIs	• Only two corticosteroid products available (QVAR and Alvesco)
pMDI + spacer	• Less need for coordination of actuation and inhalation compared with a pMDI alone • Reduced oropharyngeal deposition compared with a pMDI alone • Improves lung deposition if this is poor with pMDI alone • Useful for maintaining efficient drug delivery during acute exacerbations • Can use tidal breathing if the spacer has a valve • Some spacers make a noise to indicate that the inhalation flow is too fast	• More expensive and less portable than a pMDI alone • Prone to reduced or inconsistent dosing because of electrostatic charge associated with plastic spacers • Special washing instructions • Some patients find inhalation with a spacer more complex and dose delivered may be lower if not used correctly • Some children like to make the noise, and if they do, they will be inhaling too fast
BA-pMDIs	• May be useful for patients who cannot coordinate inhalation and actuation; may be useful for the elderly • Should not be used with a spacer	• Patients sometimes stop inhaling once actuation occurs • Can only be used with a drug that is dispensed with the device; no substitutions
DPIs	• Portable and compact; many are multi-dose • Some are single-dose with doses kept separately in sealed package • Breath-actuated, so no need to coordinate actuation and inhalation, which is required with a pMDI • Most multi-dose devices have a dose counter	• Single-dose devices require repeat loading, which can lead to error; two separate inhalations are required for each dose • DPI delivery can result in high oropharyngeal deposition because a forceful inhalation is needed to aerosolize the particles • Flow-dependent dose emission for some designs; poor quality (or no) dose emitted if inspiratory flow is too slow • Patients need to exhale into the room to functional residual capacity before inhaling from the DPI; patients should not exhale into the device once the dose has been prepared for inhalation, or the dose could be blown out of the devices • Must be upright when preparing the dose for inhalation; must be kept upright or turned horizontally for inhalation • Need to be stored in cool, dry place

Abbreviations: BA-pMDI, breath-activated pMDI; DPI, dry powder inhaler; HFA, hydrofluoroalkane; pMDI, pressurized metered dose inhaler.

FIGURE **Algorithm for choice of inhaler device for patients with asthma[1]**



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In addition to the availability of breath-actuated devices, other advances are aimed to improve adherence, ease of use, or enhanced deposition of drug particles within the lung. Examples are meters that show how much medication is left and devices that provide feedback to the patient regarding administration technique.[11]

INDIVIDUALIZING THERAPY

An important factor to consider in selecting an oral or intranasal inhaler is patient preference, which can be classified in terms of operational use (eg, ease of learning to use, holding and operating, cleaning, etc), convenience (eg, size, shape, weight, etc) and oral sensation (eg, taste and irritation). Among these, the patient's ability to generate a sufficient (>30 L/min) inspiratory flow rate and to coordinate inhaler actuation and inspiration are critical (**FIGURE**).[1] For example, in patients with sufficient inspiratory flow but poor coordination, a traditional pMDI alone would not be sufficient and options would include a breath-actuated pMDI, a DPI, or a traditional pMDI with a spacer. Patients who cannot inhale medications consciously, such as elderly patients with cognitive limitations, may be limited to a traditional pMDI with a spacer or a nebulizer.[1] A traditional pMDI with a spacer may be preferred for children, particularly if younger than 7 years of age.[29] Younger patients may prefer smaller, more technical delivery systems while older or disabled patients may benefit from larger devices that can be handled more easily and have clearer displays and larger actuators.[10] Should a patient require more than 1 inhaler, it is suggested to use the same type of inhaler device.

SUMMARY

Inhaled medications are important treatment options for asthma and allergic rhinitis. Selecting among the different formulations and delivery devices is important as it impacts adherence and proper use, both of which affect health-related outcomes. The wide variety of inhalers now available allows individualizing inhaler selection. ●

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