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A SPECIAL SUPPLEMENT ON

HOT TOPICS in Primary Care 2025

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Introduction

Primary care clinicians need to stay abreast of the vast scope of diseases we are expected to manage, which has been no different over the past year. New approvals, new data, and changing best practices continue to challenge clinicians to remain up to date. To help you be aware of the latest advances in key areas of primary care, *Hot Topics in Primary Care 2025* compiles targeted articles on multiple disease states relevant to your practice.

The emphasis on metabolic disorders is becoming more common, and primary care clinicians often are the first to diagnose and treat patients with conditions such as type 2 diabetes (T2D) and obesity. You'll find multiple articles in this supplement detailing the nuances of obesity management in primary care, as well as new and emerging information surrounding continuous glucose monitoring (CGM). Additionally, you'll learn how to identify and treat hypercortisolism, a common cause of difficult-to-treat T2D, and reducing excessive effects of endogenous cortisol can be a significant breakthrough for patients with difficulty achieving glycemic control despite standard of care treatment.

Updates in chronic respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD) are discussed in detail, reflecting their frequent occurrence in primary care settings. Primary care clinicians often treat patients who have so-called "mild" asthma—but in one article, you'll learn why this is often a misnomer, and how to make adjustments to your practice to better align with current evidence. You'll also find a detailed discussion of the relationship between COPD and cardiovascular disease, and how to mitigate cardiopulmonary risk in these patients.

With new treatments, new tests, and new data, you likely have patients with or at risk for Alzheimer disease asking what you know about these advances. The article about treating Alzheimer disease will help you better understand and apply these advances in your practice. Finally, you'll learn about a new class of treatments for gastroesophageal reflux disease (GERD), signifying the first innovation for this disease in decades.

Each piece in this special issue is crafted to offer practical, actionable insights that can be readily applied to improve patient outcomes in your health care setting. Whether you are seeking to fine-tune obesity management in your practice, improve your ability to implement and interpret CGM, reduce cardiopulmonary risk in COPD, identify and treat hypercortisolism in difficult-to-control T2D, improve outcomes for patients with mild asthma, or learn about new treatments for GERD, this supplement offers the tools and information to support your ongoing commitment to delivering high-quality patient care in you practice.

We hope that this collection of articles in *Hot Topics in Primary Care 2025* will serve as a valuable resource for continuing education and clinical practice.

A special bonus: Primary Care Metabolic Group is offering a free CME webinar on one of the topics featured in this issue, hypercortisolism. Just visit https://www.pcmg-us.org/webinar/h2c or use the QR Code in the image below.

May you and your patients enjoy continued well-being and good health.

Stephen Brunton, MD, FAAFP, CDCES
Executive Vice President
Primary Care Education Consortium

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Breaking Through Difficult-to-Control T2D: Targeting Hypercortisolism

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KEY TAKEAWAYS

- A diagnosis of hypercorticolism is missed or delayed in many patients, especially in those with difficult-to-control type 2 diabetes (T2D).
- In a certain group of patients with T2D, the prevalence of hypercortisolism may be as high as 24%.
- Primary care practitioners (PCPs) can identify patients at risk for hypercortisolism using effective screening tools to detect the disease.
- PCPs can initiate referrals to endocrinology as part of the healthcare team; additionally, PCPs can recommend and manage certain hypercortisolism treatments for eligible patients.
- Treatment for hypercortisolism may involve surgery for eligible patients and medical therapy for those who are not candidates, who decline surgery, or who have had unsuccessful surgeries.
- Treatment with a glucocorticoid receptor antagonist has shown significant reduction in glycated hemoglobin in patients with hypercortisolism and difficult-to-control T2D.

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INTRODUCTION

Endogenous hypercortisolism, also known as Cushing syndrome, is a multisystemic endocrine disorder characterized by prolonged excessive cortisol activity.[1] This condition often goes undiagnosed or is misdiagnosed, resulting in unnecessary progression of morbidity and increased cardiovascular-related mortality.[2-5] Hypercortisolism can be classified into 2 main categories:

- ***ACTH-dependent hypercortisolism:*** Includes excess adrenocorticotropic hormone (ACTH) secretion by pituitary tumors (Cushing disease) and nonpituitary tumors (ectopic ACTH secretion)
- ***ACTH-independent hypercortisolism:*** Includes autonomous cortisol secretion by one or both adrenal glands

Hypercortisolism presents with a broad spectrum of symptoms and comorbidities.[6] Although overt features such as a rounded face, central obesity, purple striae, and proximal muscle wasting are still observed in some cases, more common symptoms include nonspecific features that overlap with frequently occurring chronic diseases.[1,7] These common, heterogeneous, and multisystemic symptoms of hypercortisolism include weight gain, diabetes, hypertension, obesity, hypokalemia, dyslipidemia, osteoporosis, kidney stones, and reproductive and psychiatric disorders.[2,3,5]

The wide spectrum of clinical signs and symptoms of hypercortisolism should be considered as a continuum, with increasing rates of cardiometabolic comorbidities and mortality occurring with more severe disease.[8] Because most cases do not present with the classically described overt features and the presentation varies among patients, hypercortisolism often presents a diagnostic challenge, leading to significant diagnostic delays of up to 10 years.[9,10] Regardless of etiology, prolonged exposure to cortisol activity can lead to increased cardiometabolic comorbidities and mortality.[2-5,8] If untreated, mortality rates in patients with hypercortisolism are 2 to 5 times higher than the general population.[11-13] Thus, early detection and management are crucial to mitigate these risks.

THE RELATIONSHIP BETWEEN HYPERCORTISOLISM AND DIFFICULT-TO-CONTROL T2D

Despite the availability of effective therapies and evidence-based guidelines, many patients with T2D do not achieve treatment goals.[14,15] Patients with T2D are frequently treated in primary care, and primary care practitioners (PCPs) often play a crucial role in ensuring optimal treatment outcomes

for these patients.[15] Traditional strategies for improving glycemic control, including tailored therapy and behavior change, may be attempted but can be inadequate for some patients.[15] This presents a challenge to T2D management, especially for those patients who fail to reach glycemic targets despite best efforts from clinicians and patients to implement and adhere to optimal therapy.

Excess cortisol increases insulin resistance and decreases insulin sensitivity, negatively impacting the metabolic defects underlying T2D.[14] This contributes to a form of T2D that is difficult to control with standard therapies.[14] Clinical studies have demonstrated the benefits of addressing excess cortisol for glycemic control in T2D and for other comorbidities, such as hypertension.[16,17] Assessing hypercortisolism in patients with difficult-to-treat T2D may represent a rational strategy for identifying those who would benefit from the treatment of hypercortisolism.

SCREENING FOR AND IDENTIFYING HYPERCORTISOLISM

Best practices for screening and identifying hypercortisolism in primary care have been discussed previously.[7,18] Guidelines recommend testing for hypercortisolism in high-risk populations, such as patients with the following characteristics[18]:

- Unusual features for their age, such as osteoporosis/fragility fracture, T2D, or hypertension in young individuals
- Multiple and unexplained/progressive features, such as worsening T2D outside of the normal progression or unexplained recent weight gain
- Adrenal mass/hyperplasia

Hypercortisolism is common in patients with difficult-to-control T2D, as recently established in CATALYST, the first prospective, multicenter, US-based, large study including >1000 patients. The aims of the phase 4, two-part CATALYST trial are to (part 1) determine the prevalence of hypercortisolism in patients with difficult-to-control T2D and to (part 2) assess the safety and efficacy of mifepristone (Korlym®, Corcept Therapeutics Incorporated) to lower glycated hemoglobin (HbA1c) compared with placebo in patients with hypercortisolism identified in part 1 who have hypercortisolism.[14]

Patients were included in part 1 of the study based on the following criteria (exclusion criteria are listed in **TABLE 1**)[14]:

- Age 18-80 years
- Difficult-to-control T2D with diagnosis ≥1 year prior defined as:
  - HbA1c 7.5%-11.5% AND
  - ≥3 antihyperglycemic drugs OR
  - Insulin plus any other antihyperglycemic drugs OR
  - ≥2 antihyperglycemic drugs AND
  - The presence of ≥1 diabetes complication (eg, retinopathy, diabetic nephropathy, and chronic kidney disease [estimated glomerular filtration rate < 60 mL/min/1.73 m^2])

TABLE 1. Exclusion criteria for part 1 of the CATALYST trial.[14]

- Type 1 diabetes
- New-onset diabetes (<1 year)
- Systemic glucocorticoid medication exposure within 3 months (excluding inhalers or topical therapies)
- Pregnancy or lactation; patients of childbearing potential should have a positive pregnancy test before dexamethasone administration
- Hemodialysis or end-stage renal disease
- Severe untreated sleep apnea
- Excessive alcohol consumption (>14 drinks/week for men, >7 drinks per week for women)
- Severe medical, surgical, or psychiatric illness
- Night shift worker (awake from 23:00 to 07:00 hours)
- Has taken any investigational drug within 4 weeks prior to screening, or within less than 5 times the drug's half-life, whichever is longer
- Diagnosed with or having treatment plans for Cushing syndrome using any of the following treatments: mifepristone, metyrapone, osilodrostat, ketoconazole, fluconazole, aminoglutethimide, etomidate, octreotide, larazotide, pasireotide, long-acting octreotide, or long-acting pasireotide
- History of hypersensitivity or severe reaction to dexamethasone

Based on these criteria, 24% of patients with difficult-to-control T2D were found to have hypercortisolism, with an even higher prevalence rate (>30%) in certain at-risk patients, such as those with cardiac disorders or those taking ≥3 blood pressure–lowering medications.[19] Three tests are commonly used to screen for evidence of hypercortisolism: the 1-mg overnight dexamethasone suppression test (DST), late-night salivary cortisol (LNSC), and 24-hour urine-free cortisol (UFC).[18,20] Each test has its strengths and limitations.[18] However, the 1-mg overnight DST, using a post-DST serum cortisol cutoff of >1.8 µg/dL, is recommended as the most sensitive first-line screening method because of its high sensitivity (up to 95%).[18] Well-known causes of false-positive DST results should be excluded before DST. It is also important to ensure adequate suppression of normal pituitary corticotroph function, indicated by serum dexamethasone levels ≥140 ng/dL, measured alongside serum cortisol post-DST.[18] The 24-hour UFC and LNSC tests are less sensitive, but an abnormally high result strongly supports a hypercortisolism diagnosis.[7] UFC and LNSC should be conducted at least twice to ensure accurate results.[7] For the interpretation of biochemical test results, it is crucial to account for the clinical index of suspicion, especially in the

context of patients' medical history and comorbidities. A computed tomography (CT) scan is a routine part of the workup for patients with suspected hypercortisolism based on test results and clinical suspicion.[18]

CURRENT TREATMENT APPROACHES FOR HYPERCORTISOLISM

Although many patients with hypercortisolism can be identified—and in some cases treated—in primary care, successful management often involves the entire healthcare team.[7] This includes primary care clinic staff such as medical assistants, nurses, physician assistants/nurse practitioners (PAs/NPs), and physicians, as well as specialists—primarily endocrinologists and endocrinology NPs/PAs. By providing comprehensive and detailed referrals, PCPs can facilitate timely and effective specialist care, ultimately improving patient outcomes. Of note, some PCPs may choose to diagnose and treat certain cases of hypercortisolism in the primary care setting, especially when access to specialists is limited. Clinicians should engage in patient care as appropriate, based on their level of knowledge and comfort in managing hypercortisolism. An approach (via checklist) for managing hypercortisolism in primary care is suggested in **TABLE 2**.

TABLE 2. Checklist for managing hypercortisolism in primary care.

Screening

☐ **Determine patients at risk for hypercortisolism**
- Unusual features for their age, such as osteoporosis/fragility fracture, T2D, or hypertension in young individuals
- Patients with multiple and unexplained/progressive features, such as worsening T2D outside of the normal progression or unexplained recent weight gain
- All patients with adrenal mass
- Adults with difficult-to-control T2D; HbA1c 7.5%-11.5% and multiple antihyperglycemic and/or ≥2 antihypertension medications and/or ≥1 diabetes complication

Testing

☐ **Select appropriate test**
- Dexamethasone suppression test (DST): most sensitive
  - Use a post-DST serum cortisol cutoff of >1.8 µg/dL
  - Ensure adequate suppression of normal pituitary corticotroph function, indicated by serum dexamethasone levels ≥140 ng/dL, measured alongside serum cortisol post-DST
- Late-night salivary cortisol (LNSC): less sensitive (must perform at least twice)
- 24-hour, urine-free cortisol (UFC): less sensitive (must perform at least twice)

Diagnosis

☐ **Interpret test results in context of clinical characteristics**
- Rule out false positives and false negatives
- Medical history and exam
- Signs of hypercortisolism: weight gain, diabetes, hypertension, obesity, hypokalemia, dyslipidemia, osteoporosis, kidney stones, and reproductive and psychiatric disorders

Treatment

☐ **Refer patient to endocrinology or treat in primary care**

☐ **Determine whether the patient is a surgical candidate**

Contraindication or preference to avoid surgery?

☐ **If surgery is not possible or not curative, consider radiation or medical therapy**
- Options for medical therapy:
  - Glucocorticoid receptor antagonists (mifepristone)
    - Improves glycemic control in patients
  - Steroid synthesis inhibitors (metyrapone, levoketoconazole, osilodrostat)
  - Pituitary-directed agents (pasireotide, cabergoline)

☐ **Ongoing follow-up and monitoring**

First-line treatment for hypercortisolism typically involves surgical resection of the causal tumor, where possible.[21,22] For patients in whom surgery is not possible or not curative, radiation therapy or medical therapy is used.[21,22] When minimally invasive adrenalectomy is not appropriate, feasible, or preferred for treating hypercortisolism, the default approach is to manage comorbidities, such as T2D, hypertension, and hyperlipidemia.[14] However, addressing these comorbidities alone, without addressing elevated cortisol, does not lower cardiovascular risk. Certain cortisol-directed pharmacotherapies that lower the effect of cortisol in patients with hypercortisolism can potentially improve T2D, hypertension, and cardiovascular risk, including in patients who are not surgical candidates or who have failed or refused surgery.[14]

Pharmacotherapy options include ketoconazole, levoketoconazole, metyrapone, mifepristone, osilodrostat, pasireotide, and cabergoline though their approved indications and mechanisms vary (**TABLE 3**).[14,21,22] Of the approved pharmacologic agents, only mifepristone antagonizes cortisol activity directly at the glucocorticoid receptor regardless of etiology, indicating its potential for addressing comorbid conditions

TABLE 3. Characteristics of select pharmacologic treatments for hypercortisolism.[14,21,22]

Drug class	Mechanism of action	Medication	Indication	Route
Glucocorticoid receptor antagonists	Competitive glucocorticoid receptor antagonist	Mifepristone	To control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have T2D or glucose intolerance and have failed surgery or are not candidates for surgery	Oral
Steroid synthesis inhibitors	11-beta hydroxylase inhibition; also inhibits other enzymes; decreases glucocorticoid and mineralocorticoid production and secretion	Metyrapone	In combination with other diagnostic tests, for the diagnosis of adrenal insufficiency in adult and pediatric patients Treatment of Cushing syndrome (off label)	Oral
	Blocks multiple steps of steroid biosynthesis through inhibition of cytochrome P450 enzymes, including a decrease in glucocorticoid, mineralocorticoid, and adrenal androgen production and secretion	Ketoconazole	Off-label use	Oral
		Levoketoconazole	For the treatment of endogenous hypercortisolemia in adult patients with Cushing syndrome for whom surgery is not an option or has not been curative	Oral
	11-beta hydroxylase inhibition	Osilodrostat	For the treatment of endogenous hypercortisolemia in adults with Cushing syndrome for whom surgery is not an option or has not been curative	Oral
Pituitary-directed agents	Somatostatin receptor agonist; corticotroph inhibition	Pasireotide	For the treatment of adult patients with Cushing syndrome for whom pituitary surgery is not an option or has not been curative	Subcutaneous, intramuscular
	Dopamine receptor modulation; corticotroph inhibition; adrenal cortex cell stimulation	Cabergoline	Off-label use	Oral

and cardiovascular risk in patients with hypercortisolism.[14] New and emerging data highlight the potential role of pharmacotherapy to address hypercortisolism in patients with poorly controlled T2D and improve HbA1c.[14] For example, data from part 2 of the CATALYST trial showed that mifepristone reduced HbA1c at 24 weeks vs placebo in patients with hypercortisolism and difficult-to-control T2D.[23]

NEW AND EMERGING DATA FOR HYPERCORTISOLISM TREATMENT TARGETING THE GLUCOCORTICOID RECEPTOR

Within the past decade, advances in therapy for hypercortisolism have offered an increasing number of medical treatments. Moreover, there have been new data focusing on treatment of hypercortisolism through targeting glucocorticoid receptors in patients with difficult-to-control T2D.

Mifepristone is a competitive glucocorticoid receptor antagonist that has been approved since 2012 to control hyperglycemia secondary to hypercortisolism in patients with endogenous hypercortisolism who have T2D or glucose intolerance and have failed surgery or are not candidates for surgery. In part 2 of CATALYST, the safety and efficacy of mifepristone to lower HbA1c compared to placebo were assessed. Patients with hypercortisolism were enrolled in part 2 of the study if they did not require further assessment for elevated ACTH and were not candidates for, or decided against, surgery.[14] Results indicate that patients who received mifepristone had a least-squares mean change in HbA1c from baseline of –1.47% (P <.001) compared with –0.15% for those assigned to placebo (P = .92; between-group difference, –1.32%, P <.001).[23]

CASE STUDY

A 46-year-old woman with hypercortisolism, T2D, hypothyroidism, chronic kidney disease (CKD), and resistant hypertension is being managed by the care team. She currently takes metformin, dulaglutide, and empagliflozin at maximum doses, as well as 2 medications for hypertension. She is not a candidate for surgery and has not received any cortisol-targeted therapies yet (medical management of comorbidities only). Recently, her HbA1c has

increased, and the care team is considering how to adjust her treatment.

Laboratory evaluations

- Glycated hemoglobin (HbA1c): 9.3%
- Fasting glucose: 158 mg/dL
- 4-hour postprandial glucose: 270-295 mg/dL, despite dietary carbohydrate control
- Morning cortisol: 18 µg/dL (normal range 10-25 µg/dL)[24]
- Post-1 mg DST serum cortisol: 3.6 µg/dL (normal range <1.8 µg/dL)[18]
- Post-1 mg DST serum dexamethasone: 415.2 ng/dL (expected range >140 ng/dL for adequate serum cortisol suppression)[25]
- LNSC (performed twice): 3.8 nmol/L, 3.2 nmol/L (normal range <2.6 nmol/L)[26]
- 1 week after positive DST:
  - ACTH: 3 pg/mL (normal range ≥9-52 pg/mL)[27]
  - Dehydroepiandrosterone sulfate (DHEAS): 20 µg/dL (normal range 32-240 µg/dL)[28]

Clinical assessment

The patient has hypercortisolism as evidenced by the positive DST (the recommended and most sensitive test), which is a likely cause of her difficult-to-control T2D. This patient was a good candidate for DST because she met the criteria for part 1 of the CATALYST trial: HbA1c 7.5%-11.5%, ≥3 antihyperglycemic drugs, ≥1 diabetes complication, and ≥2 antihypertension medications. She did not meet any exclusion criteria (**TABLE 1**).

The diagnosis is also supported by other tests. LNSC may be preferred over UFC because of better accuracy, easier administration, and measurement of serum-free biologically active cortisol. Of note, the LNSC test is not a good option for a patient who is a shift worker or has an erratic sleep schedule. Furthermore, UFC is not an appropriate test for patients with CKD. The ACTH and DHEAS tests 1 week after the positive DST help confirm the findings and support a referral to endocrinology.

Treatment considerations

The patient was managed in primary care by her PCP, who felt comfortable diagnosing and treating hypercortisolism. However, referring the patient to endocrinology would also be an appropriate action in this scenario. The patient received a CT scan of the abdomen with adrenal protocol during workup to help determine whether she was a surgical candidate. The CT scan revealed an incidentaloma.

Because the patient prefers to avoid surgery and radiation therapy, medical management of hypercortisolism is the most likely approach to address her elevated cortisol and improve associated comorbidities. Although several medical treatment options are available, initiation of a glucocorticoid receptor antagonist such as mifepristone is the most appropriate choice because of the potential for improvement in T2D, supported by data from the recent CATALYST study. Six months after initiation of mifepristone, the patient's HbA1c improved to 7.8%, and her blood pressure also improved.

Clinical learning

This case highlights the importance of screening for hypercortisolism in patients who are at risk, particularly those with difficult-to-control T2D. Early identification and management of elevated cortisol led to improvements in the patient's T2D and hypertension. The consequences of failure to identify hypercortisolism include prolonged exposure to elevated cortisol, increasing cardiovascular risk and worsening associated comorbidities.

BOX 1. Call to action for PCPs—hypercortisolism and T2D.

- Keep in mind the effect that hypercortisolism has on blood glucose control—especially given that the prevalence of hypercortisolism in a certain group of patients with T2D is as high as 24%.
- Raise clinical suspicion of hypercortisolism when patients have difficult-to-control T2D and comorbidity despite standard-of-care treatment (multiple antihyperglycemic/ antihypertensive medications) and appropriate lifestyle adjustments.
- Screen with an overnight 1 mg DST (the most sensitive test), excluding known causes for false-positive results.
- Be prepared for proper treatment and/or referral for patients with positive test results and a high clinical suspicion for hypercortisolism.

SUMMARY

Awareness and understanding of hypercortisolism are essential for PCPs to improve the care of these patients, specifically those with difficult-to-control T2D. Recognizing the signs and symptoms, selecting patients with a high pretest probability, using appropriate screening methods, and making informed referrals can significantly impact patient health by reducing the delay in diagnosis and preventing the severe complications associated with this condition. A specific call to action for PCPs is detailed in **BOX 1**. PCPs can be empowered to increase the detection of hypercortisolism in their patients who are at risk and initiate appropriate treatments to ensure optimal patient outcomes. ●

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Beyond PPIs: New Options for Treating GERD

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KEY TAKEAWAYS

- Gastroesophageal reflux disease can be classified as nonerosive reflux disease (NERD) and erosive esophagitis (EE).
- Both NERD and EE cause significant health impacts and reduced quality of life and require accurate diagnosis and effective treatment.
- Proton pump inhibitors (PPIs) have been frequently used for treatment of NERD and EE. Although they are often effective, some patients have inadequate symptom relief and—in EE—incomplete healing and subsequent relapse.
- Potassium-competitive acid blockers (PCABs) such as vonoprazan, currently the only approved PCAB in the United States, are alternatives to PPIs. They produce more effective and long-lasting inhibition of gastric acid secretion.

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INTRODUCTION

Acid-related gastrointestinal disorders encompass a variety of diseases affecting the esophagus, stomach, and duodenum. Of these, gastroesophageal reflux disease (GERD) is one of the most common, with an estimated prevalence of 21% in the United States[1]: approximately 45 million adults have nonerosive reflux disease (NERD), and 20 million have erosive esophagitis (EE).[2] Although NERD is more common, EE has received more attention over the years. EE is estimated to be present in 25% to 50% of individuals with GERD symptoms.[3]

The pathophysiology of GERD includes dysfunction of the lower esophageal sphincter, impaired esophageal clearance, and changes in esophageal mucosal integrity. EE can develop as acidic gastric juice refluxes into the esophagus, where it may activate inflammatory responses. Additional factors that may be involved in some patients with GERD include delayed gastric emptying, decreased or inadequate salivary production, and esophageal hypersensitivity.[4] It can be challenging to establish the diagnosis of GERD accurately. EE and NERD can be classified and distinguished only by endoscopy. The management of GERD is based on patients' symptoms and, for EE, on the extent of esophageal mucosal involvement seen at endoscopy.

In addition to EE and NERD, another manifestation of GERD is Barrett's esophagus, in which the normal squamous mucosa of areas of the distal esophagus is replaced by specialized columnar epithelium (a form of intestinal metaplasia).[5] Barrett's esophagus is a complication of chronic EE and is a major risk factor for the development of esophageal adenocarcinoma.[6]

Although many patients with NERD or EE can be managed with existing treatments, gaps in care still exist. Proton pump inhibitors (PPIs) are frequently used to treat NERD, but up to 40% of patients with NERD continue to be symptomatic even when receiving standard therapy.[7] In some patients with EE, symptom resolution and complete mucosal healing on PPI treatment continue to be inadequate. Up to 15% of patients with EE do not achieve complete mucosal healing after 8 weeks of standard PPI treatment, and approximately 45% exhibit residual symptoms while receiving standard PPI therapy.[8] EE recurrence is almost inevitable if PPI treatment is interrupted, making continuous maintenance treatment essential for most—if not all.[9] Additional challenges with adequate treatment of NERD and EE include suboptimal adherence to treatment regimens and inadequate acid suppression.[4,9,10] The symptoms of GERD

are nonspecific, leading to misdiagnosis in some patients. In such patients, symptoms are related to cause(s) other than acidic gastroesophageal reflux, highlighting the need for accurate diagnosis. "Cycling" of PPIs is a common practice but unlikely to lead to improved outcomes for patients whose symptoms were refractory to a PPI.[4]

PPIs have been the mainstay for the treatment of GERD because they inhibit gastric acid secretion.[4] However, a new class of gastric acid–inhibiting drugs, potassium-competitive acid blockers (PCABs), has recently emerged with the potential to change the treatment landscape of GERD. In November 2023, the US Food and Drug Administration (FDA) approved vonoprazan as the first PCAB in the United States for EE. This marked the first innovation in approximately 30 years of drugs marketed for EE.[11] In July 2024, vonoprazan was subsequently also approved for relief of heartburn associated with NERD.[12]

GERD is one of the most common diseases seen by primary care practitioners (PCPs) and gastroenterologists.[4] PCPs should seek to implement evidence-based, best-practice approaches as recommended by clinical guidelines and recent data, referring patients to a gastroenterologist when appropriate. PCABs were not considered in the most recent clinical guidelines for the treatment of GERD.[4,13] However, this simply reflects the fact that there was no available evidence from US-based clinical trials at the time of guideline generation. Because current guidelines do not discuss where PCABs fit in the GERD treatment paradigm, clinicians need additional information to understand the clinical profile of PCABs and their appropriate place in clinical practice.

CASE STUDY 1

A 32-year-old woman with a history of irritable bowel syndrome has been self-treating her presumed GERD symptoms with over-the-counter (OTC) histamine-2 (H2)–blockers and OTC PPIs with only minimal improvement.

Clinical assessment/learning

The clinician should ask the patient to describe her symptoms in detail. The most common symptoms of GERD are heartburn and regurgitation. Heartburn is a retrosternal discomfort that is often worsened by eating. Regurgitation is the effortless return of gastric contents into the esophagus and, possibly, the throat. Both of these symptoms are experienced in the chest. However, many patients often perceive other symptoms—such as upper abdominal discomfort—as "heartburn." Patients with upper abdominal discomfort probably have dyspepsia rather than GERD and are much less likely to have symptom improvement with an acid-suppressing medicine. The clinician should also inquire about the patient's treatment history (eg, medications, dosage, frequency, and delivery mechanism).

EVALUATION AND DIAGNOSIS OF GERD

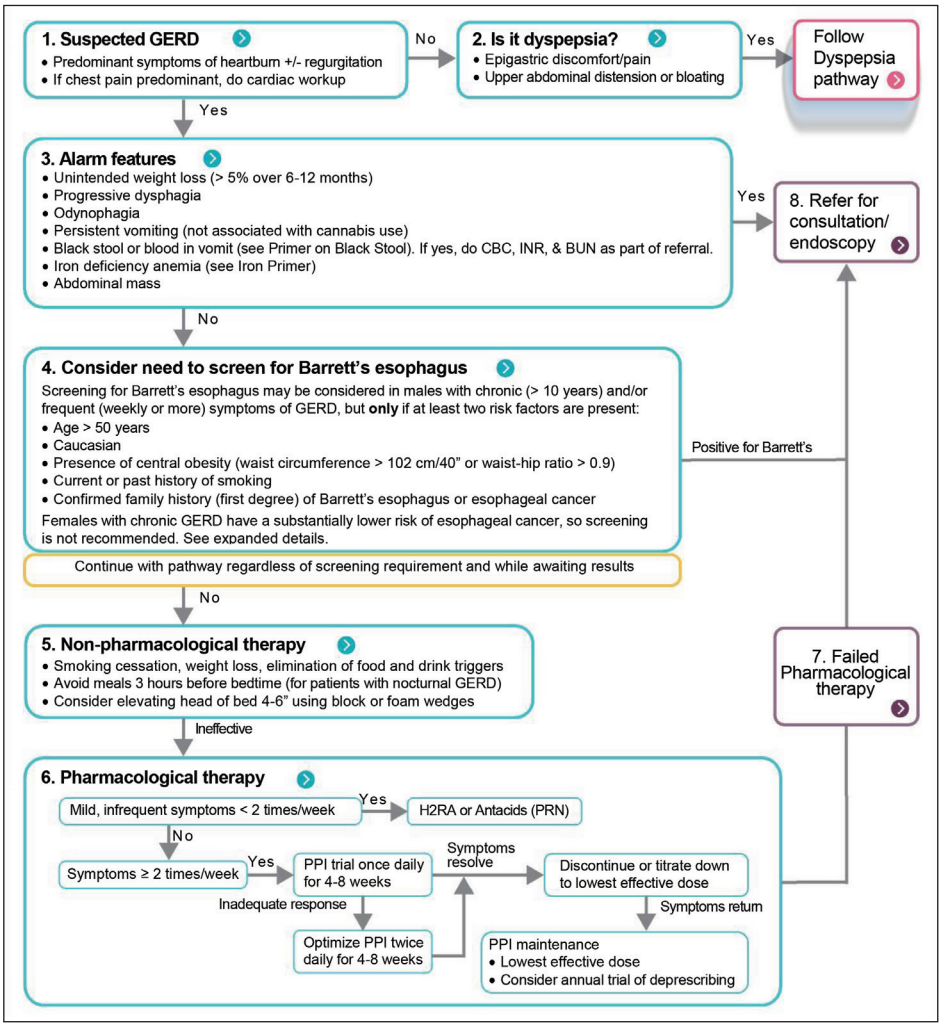
Clinicians sometimes view GERD as synonymous with heartburn (as described previously). However, GERD is more than one symptom; it is a disease that must be accurately diagnosed and effectively managed.[14]

In GERD, the patient journey usually begins with the identification of the typical symptoms of heartburn and regurgitation. Since these are common to both EE and NERD, the diagnosis of EE can be established only by an upper endoscopy that demonstrates mucosal breaks (erosions) in the distal esophagus. For patients with typical GERD symptoms occurring more than twice per week and no "alarm" features (such as dysphagia, unexplained weight loss, or gastrointestinal bleeding), an 8-week trial of empiric PPI therapy is appropriate.[4] A diagnostic algorithm for GERD is available in the 2022 American College of Gastroenterology (ACG) guideline to assist clinicians with diagnosis.[4] Patients with chest pain (and in whom heart disease has been excluded) or alarm symptoms at presentation, as well as those with multiple risk factors for Barrett's esophagus should receive objective testing for GERD via endoscopy and/or reflux monitoring.[4] Upper endoscopy is the only method for identifying EE or Barrett esophagus.[4] Algorithms for the evaluation and management of GERD in primary care have been proposed; an example is shown in **FIGURE**.[4]

EE is graded using the Los Angeles (LA) classification. This has four grades (A-D), with A being the least severe and D the most severe.[15,16] EE that is LA grade A is not considered sufficient for a definitive GERD diagnosis because it is not reliably differentiated from normal mucosa and can occur in healthy individuals without GERD symptoms.[17] EE that is LA grade B is considered diagnostic of GERD when accompanied by typical symptoms and PPI response.[4] EE that is LA grade C is nearly always diagnostic of GERD, and EE that is LA grade D is considered a manifestation of severe GERD. Patients with EE that is LA grades C and D should undergo endoscopy after PPI treatment to ensure healing and to evaluate further for Barrett's esophagus, because it may not be detectable when severe EE is present. Notably, if patients undergo endoscopy while taking a PPI, the diagnosis of EE may be missed due to mucosal healing from PPI therapy.[4]

Patients with EE who do not achieve complete healing with PPI treatment are predisposed to long-term complications.[6] More severe grades of EE (typically LA grades C and D) are more difficult to heal even with PPI therapy. Up to 30% of patients with EE that is LA grade C or D have incomplete healing with a PPI and may be at risk of progression to Barrett's esophagus.[6,18] Even with resolution of esophagitis, many patients continue to experience heartburn or regurgitation.[19]

FIGURE. Example GERD management pathway for primary care.[4]



Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; H2RA, histamine 2 receptor agonist; INR, international normalized ratio; PRN, as needed.

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MANAGEMENT OF GERD IN PRIMARY CARE: NERD AND EE

Although current guidelines recommend PPI treatment for symptomatic relief in NERD, up to 40% of patients with suspected NERD do not respond adequately.[7,20] PPIs are also recommended for control of symptoms and healing in EE.[8] However, despite recommendations for long-term maintenance in EE, PPIs often do not achieve optimal outcomes.[8,9] Additionally, reports suggest that overall management of EE remains suboptimal, often leading to cycling of PPIs, which is frequently ineffective and may delay effective treatment; there has been a long-standing need for better therapies.[6,8,9]

In addition to the need for initial healing of esophageal erosions, patients with EE almost always require long-term maintenance therapy.[9] After stopping maintenance treatment, up to 90% of patients with EE relapse within 6 months—and many relapse sooner than that.[21,22] Relapse rates of up to 41% are seen in patients with EE of LA grade D despite receiving maintenance PPI therapy.[23] Considering the burden of low healing rates, high relapse rates, and persistence of symptoms, alternative therapies are needed.

The potential role of PCABs in GERD management

PCABs are a new class of acid-suppressing agents. Compared to conventional doses of PPIs, they have a faster onset of action and produce more potent inhibition of gastric acid secretion.[24,25] PCABs that are currently available or in development around the world include vonoprazan, tegoprazan, fexuprazan, keverprazan, revaprazan, linaprazan glurate, and zastaprazan.[26] PCABs have been studied for various acid-related disorders including NERD and EE.[24,26]

Although guideline recommendations for PCABs in the United States are limited because they were published prior to the first US approval of a PCAB, practical suggestions for real-world implementation in clinical practice may offer additional insights. For example, experts suggest that PCABs may address unmet needs in patients with GERD, such as those who do not adhere to PPI dosing recommendations with regard to meals, have uncontrolled nocturnal symptoms, or experience moderate-to-severe EE.

PCABs: Mechanism of action

The mechanism of action of PCABs differs from that of PPIs.[26] As with the PPIs, PCABs inhibit the hydrogen potassium (H+/K+) ATPase on the luminal membrane of parietal cells. Although they share the same target, PCABs produce their effect by a different mechanism. PCABs are absorbed systemically and concentrate in parietal cells. They bind ionically to the potassium channel of H+/K+ ATPase to disrupt

acid secretion. Unlike PPIs, PCABs are not pro-drugs and do not require acid activation or chemical conversion before they are active. Also, unlike PPIs, they do not require any form of enteric coating and do not need to be taken at any particular time with respect to meals. They act rapidly on the proton pump.[27] PCABs demonstrate more rapid and potent acid suppression than conventional (approved) doses of PPIs and have a longer duration of action.[28,29] Additional differences between PCABs and PPIs are noted in **TABLE**.[26]

TABLE. Comparison of characteristics of PCABs and PPIs.[26]

Characteristic	PCABs	PPIs
Prodrug	No	Yes
Acid stability	Yes	No
Inhibition and binding	Reversible, ionic	Irreversible, covalent
Half-life	6-9 hours (vonoprazan)	1 to 2 hours
Significantly affected by CYP2C19 polymorphism	No	Yes
Optimal administration	Independent of meals	30 to 60 minutes prior to mealtimes (for most PPIs)

Abbreviations: CYP2C19, cytochrome P450 2C19.

Vonoprazan efficacy data for treating NERD and EE

The approval of vonoprazan for treatment of heartburn associated with NERD is based on results of a phase 3 trial, PHALCON-NERD-301.[30] This trial included patients with NERD who experienced heartburn 4 or more days of the week, with most patients having 6 to 7 days of symptoms per week. Patients were randomized to vonoprazan 10 mg or placebo. Patients receiving vonoprazan had significant improvement of heartburn compared with those taking placebo through week 4 of the trial. The mean percentage of heartburn-free days was 45% for vonoprazan and 28% for placebo (P <.001); median percentages of 24-hour heartburn-free days were 48% (vonoprazan) and 17% (placebo).[30]

A phase 2 study, PHALCON-NERD-201, compared vonoprazan and placebo as episodic treatments for heartburn. It found significant improvement in heartburn relief 1 hour after dosing of vonoprazan. Furthermore, vonoprazan was associated with relief of significantly more heartburn episodes than placebo.[31] In an earlier study of 26 patients with PPI-resistant NERD, 69.2% reported an improvement in symptoms when switching from a PPI to vonoprazan, 23.1% reported no change in symptoms, and 7.7% reported an exacerbation of symptoms.[32] The change to vonoprazan was significantly associated with improved self-reported symptoms (odds ratio 9.0, P <.001).[32]

The phase 3 PHALCON-EE trial assessed EE healing in patients across the United States and in 7 European countries.[3] A total of 1024 patients were randomized to vonoprazan 20 mg once daily or lansoprazole 30 mg once daily for up to 8 weeks. Results demonstrated the noninferiority of vonoprazan to lansoprazole for EE healing at week 8 (93% vs 85%) and higher rates of healing at week 2 (74% vs 68%). For healing of EE of LA grades C and D, vonoprazan was superior to lansoprazole at week 2 (70% vs 53%).[3] Furthermore, a recent analysis reviewed data from trials on various PPIs, H2 blockers, and PCABs, and noted that PCABs provide the longest duration of intragastric pH >4, the highest predicted healing rates for EE, and the greatest probability of achieving healing.[33]

In Asian populations, vonoprazan, tegoprazan, and keverprazan have demonstrated noninferiority to PPIs for treatment of EE in phase 3 trials.[34-36] A smaller study has also identified successful healing with vonoprazan in patients with EE refractory to PPIs.[37] Higher healing rates with vonoprazan than lansoprazole were observed at week 2 (90% vs 79%), week 4 (96% vs 91%), and week 8 (99% vs 95%).[38] Several analyses have shown specific benefits of PCABs compared to PPIs for the healing of severe EE in Asian populations. In patients with LA grade C or D esophagitis, higher rates of mucosal healing with vonoprazan vs PPIs were observed (vonoprazan vs lansoprazole, 84.0% vs 80.6% in 1 study; 98.7% vs 87.5% in another study).[35,38]

Vonoprazan safety data

Most safety data for PCABs relates to vonoprazan, which has demonstrated short- and medium-term safety comparable to placebo or PPIs.[26] In PHALCON-NERD-301, although overall adverse events were somewhat higher in the vonoprazan groups, the drug was generally well tolerated.[30] Nausea was more common in those receiving vonoprazan than those receiving placebo.[30] In PHALCON-EE-301, rates of adverse events were similar between those receiving vonoprazan and those receiving lansoprazole.[3] A dedicated phase 4 trial (VISION) evaluated the safety profile of vonoprazan and lansoprazole over 5 years in 208 Japanese patients (139 taking vonoprazan, 69 taking lansoprazole) with healed EE.[39] After 5 years, significantly more patients taking vonoprazan (97.1%) compared with lansoprazole (86.5%) had parietal cell hyperplasia and foveolar hyperplasia (14.7% vs 1.9%). The clinical significance—if any—of these differences is unknown.

Analyses of multiple trials have indicated the safety profile of vonoprazan is consistent and comparable to PPIs for treatment-emergent adverse events.[40,41] An integrated anal-

ysis of 14 clinical trials of vonoprazan in multiple countries reported similar rates of adverse events for vonoprazan and PPIs. Both vonoprazan and PPIs had higher rates of serious adverse events (serious infections, gastrointestinal disorders, neoplasms, hepatobiliary disorders, cardiac disorders, and others) compared with placebo per 100 person-years (10.39 for vonoprazan, 10.65 for PPIs, and 1.69 for placebo).[41] Additionally, a meta-analysis comparing vonoprazan to PPIs for GERD also found similar safety outcomes, with a nonsignificant risk ratio for adverse events of 1.08 (95% CI, 0.96-1.22) for vonoprazan vs PPIs.[40]

Incorporating PCABs into clinical practice

Incorporating newer interventions in clinical practice is often a slow and challenging process, even when the intervention is evidence based. Slow uptake of novel, effective drugs can delay improvements in patient health outcomes and healthcare efficiency.[42,43]

The ACG and American Gastroenterological Association (AGA) guidelines on GERD were published before any PCABs were approved by the FDA. Both recognized that greater acid suppression might be required for patients who have inadequate response to PPIs.[4,13] With the FDA approval of vonoprazan, the data support the potential role of this agent in certain patients with GERD[44]:

- ***NERD:*** Vonoprazan is approved for the relief of heartburn associated with NERD in adults.[12] In theory, patients with NERD who have partial (but incomplete) response to a PPI may benefit from switching to a PCAB, although this has not been demonstrated in controlled studies.
- ***EE:*** Vonoprazan is approved for the healing and maintenance of all grades of EE, and relief of heartburn associated with EE in adults.[11] Patients with moderate-to-severe EE may derive particular benefit from vonoprazan, as it has higher rates of healing and maintenance of severe EE than PPIs.[3]

In a study evaluating the real-world perspectives of physicians and patients regarding EE, medications that work quickly were most important to patients. Physicians identified that faster healing is important and that better initial symptom relief would help improve adherence to therapy. Additionally, longer-lasting effects and better long-term maintenance for EE were key preferences among patients and physicians.[8]

As with many novel agents, access to and cost of vonoprazan may be challenging for some patients. Clinicians must work with insurance companies by completing prior authorizations and other requirements for coverage, as well as be aware of additional savings opportunities through copay cards that reduce out-of-pocket costs. Engaging clinic staff in helping with access issues can expedite the removal of barriers to implementing PCAB therapy for eligible patients.

CASE STUDY 2

A 59-year-old overweight White man with a previous diagnosis of EE is currently taking a once-daily PPI with incomplete heartburn relief. He undergoes esophagogastroduodenoscopy (EGD) on the recommendation of his gastroenterologist. The EGD shows that he has EE that is LA grade B and no evidence of Barrett's esophagus. He is switched from a PPI to a PCAB.

Clinical assessment/learning

There were 2 valid reasons for performing endoscopy in this patient. First, he was symptomatic despite taking a PPI once daily. Second, he had risk factors for Barrett's esophagus: male, White, and overweight, and he had a history of heartburn. Endoscopy was appropriate to exclude another cause for his symptoms aside from EE and to help to rule out Barrett's esophagus. (He had a previous diagnosis of EE; although we do not know the grade. Barrett's esophagus could have been missed if severe EE had been present.) Endoscopy showed mild EE (LA grade B). Because this was present despite taking a PPI once daily, switching to a PCAB was appropriate. Studies have shown superiority of PCABs over approved maintenance doses of PPIs in preventing endoscopic relapse of EE during maintenance treatment.

SUMMARY

Many individuals experience symptoms of GERD. The presentation of "heartburn" does not necessarily point to the diagnosis of GERD, as heartburn may have causes other than acidic reflux. Heartburn may, however, be a feature of either NERD or EE. Both can have a significant impact on patient lives, leading to problems such as loss of productivity and—in EE—the potential for serious long-term consequences. Because we cannot be certain which patients truly have GERD as a cause of their symptoms, adequate assessment is essential in all patients.

Optimal management of patients with NERD or EE in primary care is essential for relieving symptoms, improving quality of life, and reducing the risk of complications. It is important to recognize that not all patients with GERD will achieve adequate symptom control with PPIs. In such cases, clinicians should be aware that a new class of acid-suppressive therapy is now available. PCABs, such as vonoprazan, offer a novel mechanism of action and may provide an effective alternative for patients with suboptimal response to standard PPI therapy. It is important for clinicians to have access to alternatives to PPIs for select patients. PCABs such as vonoprazan may fill a clinical need for improved outcomes through more effective and long-lasting inhibition of gastric acid secretion. ●

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Comprehensive Obesity Management Part 1: Assessment and Initiation of Treatment

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KEY TAKEAWAYS

- The pathophysiology of obesity is complex and involves interactions among genetics, environment, hormones, and neural pathways regulating appetite and energy expenditure.
- Body mass index is a screening tool but is not an optimal diagnostic tool. Obesity treatment decisions should be clinically based with the goal of improving health through weight loss.
- Comprehensive obesity management includes addressing psychosocial factors (eg, weight stigma and internalized weight bias), lifestyle behaviors (ie, nutrition, physical activity, stress, and sleep), behavioral therapy, and consideration of obesity medications and/or metabolic and bariatric surgery.
- Approved obesity medications include phentermine, orlistat, phentermine/topiramate extended release, naltrexone sustained release (SR)/bupropion sustained release, (SR), liraglutide, semaglutide, setmelanotide, and tirzepatide.
- Selection of treatment options should be based on the burden of disease to the patient. The goal of treatment is to prevent and/or improve complications and to reduce the burden of obesity.
- Considerations when selecting obesity medications include evaluating: adverse effects, contraindications, or potential drug-drug interactions; whether improvements in other symptoms or comorbidities can be achieved with obesity medications selected; and desired weight loss to achieve clinical improvements.
- Patient preferences, cost, and insurance coverage are considerations for all treatment approaches.
- Use person-centered language and the 5As (ask, assess, advise, agree, assist) in developing and modifying the comprehensive obesity management plan. Additionally, set the expectation on the need for continued individualization of the management plan and long-term treatment.

Once treatment options are agreed upon, ensure the patient understands rationale for treatment, treatment recommendations, and intended outcomes. It is important to provide education and referrals to resources for long-term support.

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INTRODUCTION

Overweight and obesity affect nearly 75% of adults in the United States.[1] Recent estimates from the Centers for Disease Control suggest a plateau in obesity rates at 40.3% from 2021 to 2023[2]; however, the obesity rate is still higher than the *Healthy People 2030* goal of 36%.[3]

Obesity is recognized as a disease and is causally linked to many other noncommunicable complications and comorbidities (eg, prediabetes, diabetes, cardiovascular disease, obstructive sleep apnea [OSA], and metabolic dysfunction-associated steatohepatitis, among others).[4,5] Overweight and obesity are often categorized using body mass index (BMI). For individuals aged 18 years and older, a BMI of 25 to <30 is defined as overweight, and a BMI of ≥30 is defined as obese. BMI is a good screening tool; however, it has many limitations as a diagnostic tool.[6-8] In clinical practice, it is recommended to add another anthropometric measure with BMI, such as waist circumference (WC), waist-to-hip ratio, waist-to-height ratio, or body fat measurement (eg, bioelectrical impedance analysis) to assess excess body fat, and utilize clinical indicators (ie, obesity-related organ dysfunction, limitations of daily activi-

ties, or both) to determine the best next steps in obesity management.[6]

Despite the long-held belief that obesity is caused primarily by excess caloric intake and inadequate calorie expenditure, obesity is more complex. It results from the relationship among environmental, social, behavioral, psychological, genetic, and biological drivers that alter hunger, satiety, and energy balance.[9,10] Within these complex factors, individual variability is driven by other influences that can affect body weight (eg, stress, weight stigma, and life transitions such as menopause).[7,9]

Given the complexity of obesity, the goal of an individualized obesity management plan is to address obesity-related health risks. Weight loss is an outcome that can contribute to improvement in those risks.[6-8] The plan should consider psychosocial factors, including weight stigma and internalized weight bias (IWB), lifestyle behaviors (ie, nutrition, physical activity, stress, and sleep), and behavioral therapy. It should also include consideration of obesity medication and/or metabolic and bariatric surgery (MBS), when appropriate.[7,8,11,12]

Primary care practitioners (PCPs) are a main source of contact for patients, and research suggests that patients do want to discuss weight management with their PCP.[13] Recent recognition of IWB and stigma[7] as contributing factors associated with obesity makes it especially important to gauge readiness and ask permission to discuss weight as part of the treatment planning. Obesity is a disease, not a lifestyle choice[7]; however, lifestyle changes are foundational to treatment. Lifestyle interventions have been demonstrated to lead to meaningful weight loss of 7% to 8.6% over 1 year[14,15] and are key components of treatment plans for obesity.[6] The growth in the number of obesity medications[11,16-18] and the clinically meaningful weight loss achieved with newer incretin-based obesity medications (ranging from 15% to 21% based on treatment estimates)[19,20] make obesity medication or MBS recommended options to improve or prevent some potentially life-threatening conditions (eg, diabetes or heart disease).[21-23] The purpose of this first of 2 articles on comprehensive obesity management is to help PCPs screen for, assess, and diagnose obesity, and initiate a comprehensive obesity treatment plan in collaboration with patients.

CASE STUDY

SB is a 55-year-old postmenopausal woman who recently scheduled an appointment with her PCP due to continuing symptoms of OSA (ie, morning headaches, fatigue, and snoring). SB has not been using a continuous positive airway pressure (CPAP) machine. She is currently taking blood pressure medication (metoprolol) and has recently started using over-the-counter (OTC) sleep aids like diphenhydramine and acetaminophen to help her sleep. She noted that over the past 10 years during perimenopause and now menopause she has gained more than 25 pounds. She also describes eating higher-calorie foods along with reduced activity, which she attributes to changes in her sleep patterns. She sleeps well for a few hours and then more intermittently unless she takes an OTC sleep aid. She reports the sleep aids leave her groggy in the morning and she is more anxious and depressed due to poor sleep habits. SB indicates that prior to perimenopause and menopause she did not struggle with her weight. She has tried to lose weight the past few years but has been unsuccessful.

Her current height is 5'4" and her weight is 175 pounds. She has not seen her PCP in a few years because she did not like how she was treated at her last visit by another clinician (ie, weighed in the office hall, improper comments about her weight, gown did not fit, physician told her to eat less as treatment for her weight without asking about her lifestyle choices). Her feelings about her treatment led her to skip preventive screenings.

DEVELOPING A COMPREHENSIVE OBESITY MANAGEMENT PLAN

The treatment of obesity has been evolving. It is now recognized that BMI is not the primary tool for diagnosing obesity.[6-8] Weight bias and stigma are linked to obesity, poor treatment outcomes and adherence,[7,8] and newer obesity medications and MBS have expanded treatment options to improve health and weight loss outcomes.[21-24] See the following guidelines and resources to inform clinicians about optimal approaches for obesity diagnosis and management:

- *The Lancet Diabetes & Endocrinology Commission: Definition and Diagnostic Criteria for Clinical Obesity* (2025).[6]
- *American Association of Clinical Endocrinology Consensus Statement: Addressing Stigma and Bias in the Diagnosis and Management of Patients With Obesity/Adiposity-Based Chronic Disease and Assessing Bias and Stigmatization as Determinants of Disease Severity* (2023).[7]
- *American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for Metabolic and Bariatric Surgery* (2022).[23]
- *Obesity Algorithm* by the Obesity Medicine Association (2024).[25]
- *Obesity Definition, Diagnosis, Bias, Standard Operating Procedures (SOPs), and Telehealth: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS)* (2022).[8]
- *Practice Manual: Addressing Health Disparities for Patients With Obesity* from the American Academy of Family Physicians (2024).[26]
- *Obesity in Adults: A Clinical Practice Guideline* from the Canadian Medical Association (2020).[27]

- American Association of Clinical Endocrinologists and American College of Endocrinology: *Comprehensive Clinical Practice Guidelines for Medical Care of Patients With Obesity* (2016).[28]

This article focuses on 5 steps to developing a collaborative, comprehensive plan for a person living with obesity. These steps are modified from the recommended guidelines and resources.[6-8,23,26,27,29] Each step will be briefly reviewed with supporting evidence. The steps correspond with the 5As framework (ask, assess, advise, agree, assist), which evidence suggests is helpful to guide discussions with patients diagnosed with obesity.[27,29]

Step 1: ASK (use a patient-centric approach to reduce stigma and treat obesity)

A patient-centered approach begins before a patient arrives at the office. Patients presenting with obesity should not experience weight bias and stigma in the clinic setting.[8] Evaluate the office setting for patient comfort. Think about privacy and where the weight scale is located, the size of the chairs in the waiting room, the available blood pressure cuff sizes, and other office features.

Prior to the patient visit, some information can be obtained by a pre-visit questionnaire completed by the patient. Clinicians should thoroughly review current and past medications in addition to medical, surgical, family, and psychiatric history, including specifically screening for untreated/uncontrolled eating disorders and substance use disorders.[11] Also include in the pre-visit survey questions on weight history and prior weight loss attempts; lifestyle history regarding eating habits; lifestyle behaviors such as nutrition, physical activity, stress, and sleep; psychosocial factors; food access; and more.[27,29]

Once your patient arrives in your exam room, it is important to do the following:

- Ask if they would like to discuss their weight during the visit. Patients who have experienced weight bias and stigma may experience higher levels of psychological disorders such as depression, anxiety, and disordered eating. As a result, it is important to ask permission to discuss their weight in the context of clinical obesity.[7,8]
- Use person-centered language in your conversation that does not label the individual by their disease.[8] Some examples are "person with obesity," "person affected by obesity." Or note in the chart the patient has obesity instead of referring to them as an obese person or large person. Acknowledge your patient's struggles and validate how they feel.

Step 2: ASSESS (diagnose obesity, identify contributing factors, and prioritize treatment plan goals)

Conduct a physical exam, and order labs and other tests based on clinical judgment. While most guidelines still recommend a BMI as a primary way of diagnosing obesity, PCPs should develop their practice to integrate another anthropometric measure, such as WC, waist-to-hip ratio, weight-to-height ratio, or a body fat measurement, such as bioelectrical impedance analysis to appropriately diagnose excess body fat.[6,7] Note that with WC, waist-to-hip, and waist-to-height cutoffs, the increased risk needs to be interpreted by clinicians using published gender- and race-specific values.[30] In addition to adiposity, an obesity diagnosis should include a clinical component, such as diagnosis of health risks and obesity-related complications.

After you assess BMI, excess body fat, and clinical indicators of obesity, a diagnosis of overweight or obesity is recommended. Include in your diagnosis an assessment of whether the patient has health risks, such as organ dysfunction and/or reduced ability to conduct daily activities.[6]

Stigma and IWB are also recognized as contributing factors to obesity.[7,8] Patients diagnosed with obesity can experience weight bias and stigma in all aspects of their lives, including healthcare settings, and this can lead to lack of follow-up, poor adherence to recommended therapies, and additional stress.[9,26] The PCP can broach the topic of weight bias and stigma by using reflective language, as in this example: "Many of my patients who live with obesity have experienced discrimination, prejudice, or emotional distress because of their weight. Have you had this experience? If so, how has this affected your mental and physical health?" This gives individuals permission to share their stories so that the PCP can better understand their lived experience. To minimize weight bias and stigma, it is important to explore the patient's readiness to focus on their health and understand their weight loss expectations before prioritizing the treatment plan recommendations. Do not assume they are ready to initiate treatment; the goal is to determine what they are ready to start.

Step 3: ADVISE (on treatment options)

To help patients improve obesity-related health risks effectively, PCPs should recommend a comprehensive strategy that incorporates a lifestyle prescription including nutrition, physical activity, aerobic exercise and strength training, stress management, and sleep, as well as obesity medication or MBS, as appropriate.

Lifestyle is the base strategy for any comprehensive obesity management plan. Long-term lifestyle intervention studies like the Diabetes Prevention Program[14] and Look Ahead[15] trials have demonstrated that lifestyle behavior changes are foundational to weight loss. Key behavioral strategies include self-monitoring of food intake, activity levels, weight, stress level, sleep habits, and others, as well as problem solving, cognitive restructuring, goal setting, and ongoing support.[14,15]

Treatment plans for obesity should consider the expected

goals of treatment. Weight loss has been demonstrated to improve obesity-related complications and comorbidities.[29]

If obesity medications are part of the treatment recommendation, **TABLE** provides a summary of current US Food and Drug Administration (FDA)-approved medications for weight loss.[18-20,24,31-34] Potential weight loss outcomes and other approved indications are also included. Considerations when choosing an obesity medication[11,29] include side effects, contraindications, or drug-drug interactions; whether a specific medication can improve other conditions or symptoms the patient is having; the desired weight loss to achieve intended health outcomes; patient preferences for administration (oral or weekly or daily injection); cost; and patient insurance coverage.

Step 4: AGREE (on treatment goals)

It is important to collaborate on treatment goals with a focus on health outcomes. However, patients will be focused on weight, so it is good to discuss expected efficacy of the selected treatment that is expressed as percentage of weight loss from highest weight as opposed to trying to achieve a specific goal weight. Ensure patients also know that once the weight loss has been achieved, it is recommended that the chosen treatment be continued to prevent weight regain. Additionally, agree upon goals for lifestyle behaviors such as nutrition, physical activity, aerobic exercise, strength training, sleep, and stress management, in addition to clinical treatment goals.

Step 5: ASSIST (with education and follow-up, including referrals)

Prior to leaving the office, ask the patient to articulate the treatment plan to ensure understanding. If obesity medication is part of the treatment plan, stress the need for long-term treatment of obesity and provide education on how to take and store the medication (oral or injection) and how to manage common adverse effects. Any food or activity considerations to mitigate medication adverse effects should also be discussed.

Ensure patients receive education and referrals for support to registered dietitian nutritionists (RDNs), behavioral health professionals, exercise physiologists, and/or other specialists. The patient should understand the desired follow-up schedule. For example, when obesity medications are part of the treatment plan, patients should be aware that more visits may be required to titrate medication doses.

CASE STUDY (CONTINUED)

SB experienced weight bias on a prior visit, which contributed to delays in seeking treatment to address health changes resulting from menopause, weight gain, and sleep issues. As part of her care, it will be important to:

- ***ASK:*** Get permission to discuss her weight in addition to discussing modifications to existing treatments.
- ***ASSESS:*** Consider screening for weight bias and stigma given initial comments about her prior clinic visit and lack of follow-up on preventive measures. Measure abdominal circumference to assess excess body fat rather than relying solely on BMI. The measurement should be at the level of the anterior superior iliac crest in a horizontal plane, after having the patient take a deep breath and then exhale. Given that diphenhydramine and metoprolol may both cause weight gain, consider making changes. Assess blood pressure control and further assess reasons for not using a CPAP machine, which could help improve sleep.

  Based on assessment, SB has a BMI of 30 and an abdominal circumference measurement >88 cm (~34.6 inches), confirming a diagnosis of obesity (excess body fat). She also has a history of high blood pressure controlled with medication, a history of OSA with an apnea-hypopnea index of 35, recent weight gain, inadequate sleep, and poor eating behaviors. Assessment confirms changes in treatment plan are necessary.
- ***ADVISE:*** Recommend SB cross-titrate from metoprolol to an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker like lisinopril for blood pressure control, and start SB on an obesity medication, specifically tirzepatide, which can also improve OSA (see **TABLE**). Encourage her to use her CPAP machine and follow up on preventive screenings. Discuss how the required foundational lifestyle behaviors, along with an obesity medication, will improve her outcomes.
- ***AGREE:*** Reach agreement on the treatment plan, including obesity medication and use of the CPAP machine. Prior to leaving the office, a nurse educator and RDN should introduce themselves.
- ***ASSIST:*** Provide SB education on the medication: dose, frequency, storage, injection instructions, and potential adverse effects. Schedule a follow-up appointment in 4 weeks and make referrals, for example, to an RDN, for ongoing education and support.

SUMMARY

Overweight and obesity are common diagnoses in primary care but often go unaddressed or undertreated. Obesity is a chronic disease that requires ongoing medical management to reduce complications and associated comorbidities. The pathophysiology of obesity is complex and involves interactions among genetics, environment, hormones, and neural pathways regulating appetite and energy expenditure. Optimal treatment for obesity starts with confirming an obesity diagnosis and requires a comprehensive approach using foundational lifestyle interventions (nutrition, physical activity, aerobic exercise, strength training, stress management, and sleep),

TABLE. FDA-approved obesity medications.[18-20,24,31-34]

Generic	Brand	Year	Mechanism of action (effects)	Dosing guideline	Percentage of total body weight loss	Other clinical considerations[a]	Most common adverse effects
Phentermine	Adipex, Lomaira	1959	Increases neurotransmitter norepinephrine (appetite regulation)	Oral: typical dosage for Adipex is 15 mg or 30 mg per day; typical dosage for Lomaira is 8 mg by mouth 3 times/day 30 minutes before meals	6.1%	Currently approved for short-term use by the FDA. State regulations may vary	Dry mouth, constipation, anxiety, and dysgeusia
Orlistat	Xenical, Alli	1999	Blocks enzyme, lipase, which breaks down fat (reduces fat absorption)	Oral: 120 mg capsule 3 times/day with fat-containing meals	9%	Not approved for any other medical conditions	Oily fecal spotting and fecal urgency
Phentermine/ Topiramate ER	Qsymia	2012	Increases the neurotransmitters norepinephrine and GABA (appetite regulation)	Oral: Qsymia (3.75 mg/23 mg) daily for 14 days; then increase to 15 mg/92 mg daily	9.8%	Topiramate is also used for seizures and migraine prophylaxis	Abnormal sensations, such as "pins and needles" sensation on skin, dry mouth, constipation, dysgeusia, and kidney stones/ nephrolithiasis
Naltrexone SR/Bupropion SR	Contrave	2014	Increases neurotransmitters, including norepinephrine and dopamine (appetite regulation)	Oral: Maximum dose: 4 tablets/ day (naltrexone 32 mg/bupropion 360 mg); start 1 tablet per day in morning week 1; week 2, 1 tablet morning and evening; week 3, 2 tablets morning and 1 evening; week 4, 2 tablets twice daily	6.1%	Bupropion is used to treat major depressive disorder and to prevent seasonal affective disorder. It also aids in smoking cessation Bupropion is also known to lower the seizure threshold Naltrexone is an opioid receptor antagonist	Nausea, constipation, headache, vomiting, dizziness, insomnia, and dry mouth
Liraglutide	Saxenda	2014	Mimics glucagon-like peptide-1 (GLP-1) (appetite regulation)	Subcutaneous injection: 0.6-3.0 mg maximum dose daily. Follow dose escalation schedule, increasing by 0.6 mg each week to maximum dose	8.0%	Also indicated to treat type 2 diabetes and heart disease to lower the risk of heart attack, stroke, or death caused by heart disease	Nausea, diarrhea, vomiting, and constipation
Setmelanotide	Imcivree	2020	Activates melanocortin-4 receptors in the brain, specifically in the paraventricular nucleus of the hypothalamus and the lateral hypothalamic area (appetite and hunger regulation)	Subcutaneous injection: 2.0-3.0 mg, once daily, for 6 years of age and older	10.0%	Patients selected for treatment should have a genetically determined deficiency of pro-opiomelanocortin, proprotein subtilisin/ kexin type 1, or leptin receptor or a clinical diagnosis of Bardet-Biedl syndrome	Nausea, headache, diarrhea, stomach pain, back pain, vomiting, depression, upper respiratory infection, and erection in males without sexual activity

TABLE CONTINUED ON NEXT PAGE

pharmacotherapy, and/or MBS when indicated. All treatment plans should align with the patient's goals and preferences.

Obesity medications may include phentermine, orlistat, phentermine/topiramate extended release, naltrexone sustained release (SR)/bupropion SR, liraglutide, semaglutide, setmelanotide, or tirzepatide. Newer incretin-based therapies have demonstrated promising results, leading to more significant weight loss and improved clinical outcomes. Their

TABLE. FDA-approved obesity medications.[18-20,24,31-34] (cont'd)

Generic	Brand	Year	Mechanism of action (effects)	Dosing guideline	Percentage of total body weight loss	Other clinical considerations[a]	Most common adverse effects
Semaglutide	Wegovy	2021	Mimics GLP-1 (appetite regulation)	Subcutaneous injection: 0.25 mg, 0.5 mg, 1 mg, and 1.7 mg weekly. Maintenance dose: 1.7 mg and 2.4 mg weekly	14.9%	Also indicated to treat type 2 diabetes and heart disease to lower the risk of recurrent events caused by heart disease	Nausea, diarrhea, vomiting, and constipation
Tirzepatide	Zepbound	2023	Mimics GLP-1 and glucose-dependent insulinotropic polypeptide receptor (appetite regulation)	Subcutaneous injection: 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg weekly. Maintenance doses: 5.0 mg, 10 mg, and 15 mg weekly	20.9%	Also indicated to treat type 2 diabetes and to improve moderate-to-severe OSA	Nausea, diarrhea, vomiting, and constipation

[a]No obesity medications are approved for use during pregnancy, so it is important to discuss adequate contraception.

safety and novel mechanisms of action make them appealing options for the treatment of clinical obesity. In part 2 of this series, we will discuss how to adjust the treatment plan for weight loss and weight maintenance. ●

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Comprehensive Obesity Management Part 2: Ongoing Assessment and Individualization of the Treatment Plan

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KEY TAKEAWAYS

- Given the complex nature of obesity, especially individual variability to treatment, it is important to assess clinical response to therapy and modify treatment plans regularly, as needed, to achieve therapeutic goals.
- Engage the entire healthcare team in the education and follow-up schedule for patients taking obesity medications to ensure effective management and continuity of care.
- Considerations when selecting, titrating, or changing an obesity medication include evaluating adverse effects and changes in other symptoms or comorbidities and the desired percentage weight loss to achieve clinical improvements.
- Common adverse effects for incretin-based obesity medications include nausea, constipation, diarrhea, and vomiting. One of the common reasons patients discontinue therapies is adverse effects. When a patient is not tolerating a dose escalation, reduce the dose or maintain the current dose to allow the patient's body to adapt to the medication. Education on effective mitigation strategies, such as eating smaller meals, will improve patient adherence to obesity medications.
- As the patient loses weight, it may be necessary to adjust doses of other therapies, such as those for diabetes or hypertension.
- Ensure patients have access to resources to support them and their treatment plan. A registered dietitian nutritionist (RDN), if available, can play a pivotal role in supporting the patient to modify behaviors, manage adverse effects, and address nutrition and hydration needs.
- Encourage patients to eat adequate protein and integrate resistance training into their lifestyle to reduce the loss of lean body mass during the weight loss process.
- Continue to set the expectation for consistent, long-term follow-up to individualize the plan to achieve the best possible outcomes.

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INTRODUCTION

The management of obesity is experiencing a transformation, both in definition and treatment options. Recent guidelines and recommendations[1-3] have expanded the thinking on the diagnosis of obesity beyond body mass index (BMI). In addition to BMI, *The Lancet* Commission recommends confirming an obesity diagnosis by measuring excess fat through another anthropometric measurement, for example, waist circumference, waist-to-height ratio, or waist-to-hip ratio, or direct body fat measurement (eg, dual x-ray absorptiometry or bioimpedance), along with the presence of obesity-related signs, symptoms, blood tests demonstrating organ dysfunction, or limitations of daily activities.[1]

The growth in pharmacotherapy options for the treatment of obesity has contributed to this transformation.[4-11] Clinically meaningful weight loss can be achieved with newer incretin-based obesity medications ranging from approximately 15% to 21%.[5,7] These therapies present primary care practitioners (PCPs) with more options to tailor comprehensive obesity treatment plans to an individual's preferences and comorbidities and to optimize treatment response.[12-14]

Obesity has been recognized as a disease,[14,15] and comprehensive obesity management should follow the same principles as other chronic diseases where treatment goals determine appropriate interventions. Individualized, patient-centered treatment plans should consider complications and comorbidities and include use of obesity medications, when indicated, to improve treatment response.[12,13] Understanding prior weight loss experiences[13,16] and engaging patients in treatment decisions is crucial to success. Weight loss and maintenance both require ongoing re-assessment and modifications of the treatment plan.[13,17] PCPs have a pivotal role in managing obesity with evidence-based interventions.

The article *Comprehensive Obesity Management Part 1* in this same issue focused on the initial evaluation and diagnosis of obesity. *Part 2* presents an overview of how to escalate, de-escalate, or change obesity medications, when to schedule follow-up visits, how to address adverse effects to increase patient adherence to treatment plans, which considerations for nutrition and physical activity changes will improve treatment outcomes, and most importantly, how to keep patients engaged for the long-term. The 5As framework (ask, assess, advise, agree, and assist) will be demonstrated through a case discussion on the key principles of engaging patients while on obesity medications. Evidence suggests the 5As framework is helpful to guide discussions with patients.[18,19] We will continue the case study of patient SB from *Part 1* to illustrate how to address management considerations as follow-up continues.

CASE STUDY

SB is a 55-year-old postmenopausal woman with a history of obstructive sleep apnea (OSA), high blood pressure, and obesity (BMI of 30 with waist circumference >88 cm [34.6 inches], confirming excess body fat). She returned 1 month after her first visit for a follow-up visit after starting on tirzepatide 2.5 mg subcutaneously once weekly. At her last visit, her blood pressure medication was changed from metoprolol to lisinopril. SB was encouraged to use her continuous positive airway pressure (CPAP) machine, received instruction on how to take her obesity and new blood pressure medication, and was referred to both a registered dietitian nutritionist (RDN) and to a sleep clinic.

At her 4-week follow-up appointment:

- ***ASK:*** Gather information from SB on how she is doing with her plan. SB reports she is taking the medication as prescribed and has re-started using her CPAP machine at night. She reports sleeping more hours each night and experiencing less daytime sleepiness. SB has her sleep study scheduled for next week. SB noted that she experienced mild nausea over the first 2 weeks of administration, which lessened after seeing the RDN, who recommended nutritional changes. She also reports her appetite has decreased.
- ***ASSESS:*** Evaluate clinically how SB is doing. Assessment reveals normal blood pressure and weight loss of 3.5 lbs (2% of body weight), which is appropriate at 4-week follow-up.
- ***ADVISE:*** Tell SB that she is doing well and encourage her to continue to focus on healthy lifestyle behaviors. SB will increase tirzepatide to the next dose of 5 mg. Encourage SB to drink fluids throughout the day and eat smaller, low-fat meals to mitigate nausea (**TABLE 1**).
- ***AGREE:*** Gain agreement on plan. SB will increase the dose of obesity medication, utilize nutrition strategies discussed to manage nausea, and continue with CPAP machine until her sleep study.
- ***ASSIST:*** Share resources on nausea and schedule a follow-up appointment with the RDN to continue to support SB in mitigating adverse effects and making high-quality food choices. Schedule follow-up in 1 month.

DEVELOPING THE PRACTICE OF REGULAR FOLLOW-UP FOR COMPREHENSIVE OBESITY MANAGEMENT

A team approach can be helpful when integrating pharmacotherapy into comprehensive obesity management; this ensures consistent follow-up with patients to individualize therapy. Leverage available office staff, such as a scheduler, dietitian, nurse, and/or pharmacist within your practice to ensure delivery of effective care in collaboration with patients. **TABLE 2** provides examples of visit scheduling and timing, key considerations for modifying medication dosage or addressing adverse effects, and components of care and education.[12,19,20] Also, see references 3 and 21 for helpful office procedures and guidance as you establish the practice of utilizing pharmacotherapies in your delivery of comprehensive obesity management. As you increase utilization of obesity medications, consider establishing protocols for initiating and titrating medications. Utilize other health professionals within your practice to support obesity medication management using established protocols[22,23] and share resources, including mobile app recommendations, to support lifestyle changes.

Advancing and adjusting obesity medications

The purpose of this section is to review key considerations as you individualize obesity medications and treatment plans to deliver comprehensive obesity management. Critical aspects of advancing and adjusting obesity medications include frequency of follow-up, monitoring the response to therapy and making changes as needed, and addressing adverse effects and lifestyle behaviors required to support the treatment plan.

Once initiated, regular follow-up (**TABLE 2**) is necessary to monitor the response to obesity medications.[12,19,20] Short interval follow up, about 2 to 4 weeks after initiation, either in-person or via telehealth, is recommended to assess tolerance, such as existence of adverse effects, and determine whether changes in the treatment plan are required to achieve the desired health outcome.

Schedule ongoing visits every month for the first 3 months or longer if you continue to titrate medication. Once a therapeutic dose has been achieved, schedule ongoing follow-up visits (approximately every 3 months) for clinical discussion,[20] checking vital signs, and determining response to weight-loss medication. Establish a protocol in your practice on the follow-up schedule and team roles related to follow-up visits. Visits could be completed via telehealth and/or with the use of other professionals within the practice by employing agreed-upon protocols.

During visits, assess weight loss progress; biometrics, such as blood pressure, glucose, and lipids; complications; comorbidities; adverse effects; psychosocial changes; and lifestyle behaviors including nutrition and physical activity.[12,19] Ensure adequate protein intake to maintain muscle mass.[19] Based on assessment, make treatment decisions, including changes to medications for obesity and/or other comorbidities.

Obesity medication: Escalation, de-escalation, or changes in medication type

Most Prescribing Information recommends gradual dose escalation. The goal is to titrate to a dose that achieves weight loss goals and is tolerable for the patient.[24] The dosage should be individualized; keep in mind the highest dose may not be the optimal dose for every patient.[12,19] Some criteria to consider in your treatment decisions include[19,24]

- Keep dose the same if the patient is experiencing adverse effects and your assessment suggests they are not ready for dose escalation. This will give their body time to adjust.
- Increase the dose (if not yet at maximum dose) if the patient is tolerating obesity medication and has not achieved weight loss goals to attain the desired health outcomes.
- Consider switching medications or initiating combination therapy if current obesity medication is not achieving desired weight loss goals, for example, <5% weight loss after 3 months at the highest obesity medication dosage, adverse effects are unmanageable, or if the patient is regaining weight.

TABLE 1. Nutrition management of gastrointestinal adverse effects.[12]

Medication adverse effect	Nutrition management strategies
Nausea	Eat regularly with smaller portions than usual
	Eat slowly
	Stop at first signs of fullness
	Limit high-fat or spicy foods
	Stay hydrated: daily fluid intake of 64 oz
	Limit consumption of sweetened beverages
Constipation	Maintain high-fiber diet of vegetables, fruits, and whole grains
	Stay hydrated: daily fluid intake of 64 oz
	Increase physical activity; reduce sedentary behavior
	Think about adding daily magnesium (250 mg-1500 mg)
	Consider a stool softener or polyethylene glycol (PEG)
Diarrhea	Avoid sugar alcohols
	Limit intake of coffee, dairy, alcohol, and carbonated beverages
	Increase fiber intake
	Stay hydrated: daily fluid intake of 64 oz

Identifying and addressing common adverse effects

Educate patients on possible adverse effects to watch out for when obesity medications are initiated and during regular follow-up visits. Emphasize that mild to moderate adverse effects are common, primarily occurring during dose escalation, and often subside over time.[24] This is essential for 2 reasons. The first is that patients may not be forthcoming in reporting adverse effects for fear of discontinuation of treatment.[12] The second reason is research findings suggest that adverse effects are a main reason for discontinuation of treatment.[25]

The most common adverse effects for incretin-based therapies (such as liraglutide, semaglutide, and tirzepatide) are nausea, vomiting, diarrhea, and constipation.[19,24] These adverse effects are dose dependent. Constipation, however, may not be transient and could last longer than other gastrointestinal symptoms.[5,26]

Once adverse effects are identified, advise patients on how to alleviate symptoms.[12,19,24] **TABLE 1** provides strategies to address nausea, constipation, and diarrhea.[12] Eating smaller meals, limiting high-fat and spicy foods, hydrating adequately, and moderating intake of alcohol and sweetened beverages are all helpful strategies for addressing adverse effects.

TABLE 2. Treatment schedule when prescribing obesity medication.[12,19,20]

Visit type	Considerations	Care team responsibilities
Initial visit (20-40+ minutes)	• Potential adverse effects or drug-drug interactions • Other medical conditions to consider when selecting obesity medication • Desired outcomes of treatment plan • Patient preferences for administration/ timing • Cost and insurance coverage	• Prescribe and counsel on medication timing, frequency, and dose • Discuss potential adverse effects and alleviation strategies • Teach administration of medication, if injectable • Set expectation for follow-up appointments for dose escalation and treatment planning • Provide brief counseling on foundational behaviors such as nutrition, physical activity (including strength training), and hydration • Refer patient to RDN or other professionals for support
Ongoing visits (in-person or virtual) 15-20 minutes monthly for 3 months by a member of the care team. Later, when no longer titrating medication, schedule visits for approximately every 3 months. Frequency of visits can be reduced after the first year	• Tolerance, appetite, and weight loss • Medication adherence • Education and support as needed to help patient maintain diet quality and continue physical activity (including resistance training)	• Titrate obesity medication to next dose, if tolerated and needed • Assess and address any adverse effects • Reinforce lifestyle behaviors and the importance of hydration • Educate on weight loss, weight plateaus, and weight maintenance, as appropriate • Make referrals as needed for ongoing support and education

Improving nutritional intake and preserving lean body mass

Obesity medications like semaglutide and tirzepatide act to reduce appetite and hunger and increase satiety, which leads to lower caloric intake.[19,27,28] As a result, it is necessary to assess patients' food choices to ensure adequate nutrient intake. Eating high-quality foods is a key strategy in all treatment plans. Encourage patients to eat high-fiber foods, such as fruits, vegetables, whole grains, and lentils; high-quality proteins, including eggs, lean meats, poultry, and seafood (up to 1.5 g per kg of body weight per day)[20]; high-quality fats, like those found in nuts and seeds; and low-fat dairy. Also encourage patients receiving obesity medications to drink adequate fluids with a target of 2 to 3 L (68-100 fluid oz) per day.[19]

Referral to an RDN is recommended to support adequate nutrition intake when food intake is decreased and to mitigate potential adverse effects.[12] The RDN can further evaluate whether the patient is developing healthful eating patterns that meet their energy, macronutrient, micronutrient, fiber, and fluid needs.[12,19] If no RDN is available, share resources and mobile apps for support.

In addition to nutrition, discuss physical activity, including strength training to reduce lean body mass loss. Weight loss, regardless of rate, leads to loss of both fat and lean mass.[19] While more research is needed on strategies to minimize the loss of lean mass, initial research findings suggest that resistance exercise can preserve lean mass during weight loss.[29]

CASE STUDY (CONTINUED)

At SB's first follow-up visit, her tirzepatide dose was increased to 5 mg. SB completed monthly visits over the next 5 months. During that time, her dose was increased to 7.5 mg and finally to 10 mg. SB is now returning for her 6-month visit.

- ***ASK:*** Discuss how she is doing. SB states that she is getting more sleep and making higher-quality food choices. She reports she feels good about the weight she has lost, and her clothes are fitting more loosely. She completed her sleep study, and as a result, the CPAP pressure has been reduced. The sleep clinic also recommended a support group. She has attended twice and received an alternative mask interface that has helped her use the CPAP machine more effectively. Her nausea resolved with the nutrition strategies recommended, and she notes she has been working with the RDN to address constipation, a prolonged adverse effect. She bought a few weights and is doing free, online, twice-weekly strength training classes at home to preserve muscle mass. She tracked her protein intake at the recommendation of the RDN and learned she was not eating adequate protein.
- ***ASSESS:*** Evaluate progress. SB's weight has decreased by 12% over 6 months. Her blood pressure has

decreased to recommended levels due to diet, activity changes, and weight loss.

- ***ADVISE:*** Encourage SB to maintain tirzepatide dosage at 10 mg. Many patients do not need to reach maximum dosage to achieve benefit. Given changes in blood pressure, advise SB to stop taking her blood pressure medication (lisinopril). Review strategies for constipation, such as exercise and adequate water intake (**TABLE 1**). SB may also consider taking a stool softener.
- ***AGREE:*** Gain agreement with the plan prior to SB departing the office.
- ***ASSIST:*** Schedule SB to return for her next visit for a blood pressure check in 2 weeks and return for a full office visit in 3 months. Share an educational handout on constipation. Encourage SB to continue her strength training, seek support from the RDN, and attend the OSA support group.

Comprehensive obesity management requires lifelong care

Obesity management requires long-term, individualized treatment. Regaining weight is common following termination of any weight loss intervention.[30,31] Long-term weight loss maintenance with obesity medications requires more research. A retrospective observational study with 4.4 years of follow-up data observed an average weight loss of 10.4%.[14] More than half of patients were on ≥2 obesity medications at their final visit. Phase 3 trials of obesity medications demonstrated sustained clinically meaningful weight loss with obesity medication compared to placebo.[32-35] Individuals with both obesity and prediabetes who received long-term treatment with tirzepatide achieved a mean bodyweight reduction of up to 20% and had lower progression to type 2 diabetes vs placebo.[35] Semaglutide use at 4 years improved weight and anthropometrics compared with placebo and was associated with fewer cardiovascular events in individuals with overweight or obesity and preexisting cardiovascular disease.[34] More long-term, real-world studies are needed to understand medication adherence and health outcomes.

As with any chronic disease, once medications are stopped, the benefits diminish. If hypertension medications are stopped, blood pressure increases. Similarly, if obesity medications are stopped, two-thirds of the weight lost is often re-gained over the following year.[5,13,36] However, for most patients, as with any chronic disease, there is heterogeneity in response. Long-term use of obesity medications along with lifestyle counseling is required to sustain healthier weight for most patients. Research suggests that incorporating exercise, especially resistance training, with obesity medications helps improve weight loss maintenance and body composition during treatment and after termination of pharmacotherapy.[36] Lifestyle behaviors are foundational to weight loss maintenance.

SUMMARY

Overweight and obesity are common diagnoses in primary care and require individualized treatment plans for each patient. Once clinical obesity is diagnosed, a comprehensive approach can be initiated using foundational lifestyle interventions, such as nutrition, physical activity, stress management, and sleep along with pharmacotherapy and/or metabolic bariatric surgery when indicated. Treatment plans should align with the patient's goals and preferences.

Many patients are aware of and interested in obesity medications, and many have concerns about adverse effects and long-term risks; therefore, it is important to address barriers prior to initiation.[37] Once medication is initiated, continue to educate patients on the adverse effects of obesity medications and potential mitigation strategies to improve adherence. Obesity medications are efficacious, and when prescribed, require consistent follow-up care to ensure patients achieve sustainable outcomes. Check in regularly with patients to prevent potential barriers to adherence. Engage others on the healthcare team to provide ongoing support between visits to ensure continuity of care. Obesity management requires lifelong care, including ongoing individualization, to achieve the best possible outcomes. ●

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Identifying and Addressing the Hidden Risks of Mild Asthma

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KEY TAKEAWAYS

- Contrary to common perceptions, mild asthma is associated with a substantial disease burden in the form of severe exacerbations, steroid exposure, and healthcare system costs.
- While patients and clinicians may refer to asthma as being mild, the lack of a clinically useful definition causes confusion and misperceptions about disease morbidity, disease severity, and appropriate management.
- Diagnosing mild asthma is often challenging, but by focusing on objective criteria, clinicians can improve the accuracy of an asthma diagnosis.
- Managing patients with mild asthma is complex, as disease severity can fluctuate over time and seasonally, due to triggers that increase inflammation, worsen symptoms and control, and lead to exacerbations.
- New treatment paradigms for mild asthma, including intermittent and mild persistent disease, emphasize the use of inhaled corticosteroid (ICS)-containing rescue therapy regimens and avoidance of short-acting beta$_2$-agonist (SABA)-only rescue regimens.
- Use of SABA-only as rescue with maintenance ICS is a treatment option for patients with mild asthma but may not be the optimal choice, as considerable evidence exists that adherence is very poor in people with intermittent symptoms.

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INTRODUCTION

Asthma is a chronic, heterogeneous disease with substantial national and global impact. The Global Initiative for Asthma (GINA) classifies asthma severities into mild, moderate, and severe disease categories, based on a retrospective definition—the treatment that is required to achieve optimal asthma control and reduce/prevent exacerbations.[1,2] Although the stepwise treatment approach advocated in the GINA report (updated annually) and the National Asthma Education and Prevention Program (NAEPP; last updated in 2020) may suggest clear demarcations between asthma severities, in clinical practice there is often overlap between symptoms and manifestations.[2,3] Notably, NAEPP classifications also include lung function and risk domains, beyond symptoms and impairment.[3] Unlike GINA, NAEPP further subdivides mild asthma into intermittent and mild persistent categories.[1,3] Mild asthma may be viewed by patients and clinicians as a low-risk disease with low symptom burden; however, evidence suggests a wide heterogeneity in outcomes and symptoms.[4] While many individuals with mild asthma are not constantly affected by their disease, certain characteristics increase the risk of adverse outcomes (**TABLE**).[2] Additionally, exacerbations are unpredictable and can even be fatal.

Despite the substantial impact of mild asthma, present definitions are limited in their clinical usefulness.[2] Furthermore, the approach to treating mild asthma has changed significantly in recent years. Current evidence-based approaches to treatment of mild asthma incorporate certain fundamental principles, such as[2]:

- Avoiding short-acting beta$_2$-agonist (SABA)-only rescue therapy and initiating therapy with an anti-inflammatory rescue (or anti-inflammatory reliever) instead
- Assessing asthma symptoms and future risk of exacerbations as 2 separate domains to guide treatment[5]

Mild asthma is of particular importance to primary care practitioners (PCPs), as most patients with mild asthma are managed in primary care settings—up to 90% of patients with asthma seen in community or primary care settings have mild or moderate asthma.[2] Recent data indicate that high symptom burden and exposure to systemic corticosteroids (SCS) are also characteristics of patients treated for mild-to-moderate asthma, not only those with severe asthma.[6] Patients with mild asthma are rarely referred to specialists;

TABLE. Factors associated with increased risk of adverse outcomes in mild asthma.[2]

Factor	Outcome
Previous or current higher treatment requirements for adequate control	Increased exacerbations
Comorbid diagnosis of COPD	Increased exacerbations Reduced quality of life
Low eosinophil count	Suboptimal response to ICS
Current smoking	Poor response to ICS Increased exacerbation risk Increased risk of lung function decline
Female	Increased exacerbations Premenstrual exacerbations Postmenopausal persistence
Obesity (BMI >30 kg/m^2)	Greater risk of persistence
Comorbidities, especially allergic rhinitis, gastroesophageal reflux, or depression	Worse symptom control
Socioeconomic determinants of health	More frequent exacerbations Avoidable but frequent courses of systemic steroids
Older age (adults)	Underrecognized disease severity Undertreatment Worse airflow limitation Poor reversibility
Inappropriate use of SABA: • >2 puffs/wk in the absence of ICS use in the first year of asthma diagnosis • 9 or more canisters of SABA per year, <100 µg of ICS daily in a maintenance regimen during the year	Progression of disease to higher treatment requirements More frequent exacerbations
Undertreatment with anti-inflammatory medications	More persistent symptoms and airflow limitation More frequent exacerbations
Recurrent wheezing or abnormal lung function early in life	More persistent airflow limitation
Occupational exposures	Worse asthma control More persistent disease
Psychosocial factors, anxiety, and depression	Worse asthma control

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; SABA, short-acting beta$_2$-agonist.

therefore, PCPs are uniquely positioned to have a significant impact on reducing morbidity and adverse health outcomes related to mild asthma.

THE MISNOMER OF "MILD ASTHMA"

Even after decades of asthma research, there is no widely accepted or uniformly applied definition for mild asthma, leading to limited utility of this term in clinical settings.[1,2,5,7] GINA recommends that the term "mild asthma" should usually be avoided in clinical practice—or if it is used, it should be accompanied with a caution that infrequent symptoms can still result in serious health outcomes, including death.[1,2] In community and primary care settings, the designation of mild asthma often refers to the frequency or severity of symptoms or exacerbations—if patients do not have daily symptoms or if symptoms are quickly relieved.[1] In clinical trials and epidemiologic studies, mild asthma is designated based on the prescribed treatment, rather than the level of asthma control. This approach assumes that the treatment was appropriate for the patient's needs, but asthma is often under-treated or over-treated.[1] The NAEPP guidelines assign mild asthma severity based on symptoms and the frequency of SABA use and delineate "mild persistent" and "intermittent" asthma, but this historical distinction was arbitrary and not evidence based.[1,3] Since NAEPP guidelines have not been updated since 2020, discussion and recommendations in this article will be focused on the GINA report, which is updated annually.

Patients may perceive their asthma as mild if their symptoms are infrequent or easily relieved by SABA; patients often interpret "mild asthma" as meaning that there is a low risk of severe exacerbations and that inhaled corticosteroids (ICS) are not necessary for disease management.[1] As a retrospective definition aligned with GINA, asthma could be classified as mild only after several months of ICS-containing treatment and only if asthma is well controlled on low-dose ICS or as-needed ICS with a rapid-acting bronchodilator. The definition could not be applied to those with partially controlled or uncontrolled symptoms taking SABA only.[1]

It has now been well established that patients with occasional or "intermittent" asthma symptoms can have severe or fatal exacerbations, and that the risk is substantially reduced by ICS-containing treatment compared with SABA alone.[1,8,9] Up to 30% of asthma exacerbations and deaths occur in people with infrequent symptoms, including patients with symptoms that occur less than weekly or only with strenuous exercise.[1] The most urgent problem with the term "mild asthma," regardless of how it is defined, is that it encourages complacency, since both patients and clinicians often interpret "mild asthma" to mean that the patient is at low risk and does not need ICS-containing treatment.[1]

CASE STUDY

A 59-year-old woman presents to her primary care clinic for an asthma follow-up visit. She is treated with SABA-only rescue therapy and has a diagnosis of mild asthma. She has had several exacerbations over the past 5 years, requiring oral corticosteroids and/or a visit to the emergency department, based on clinical records. When asked about her asthma control, the patient responds that most days she doesn't even know she has asthma, but she uses her rescue inhaler about twice a month on "really bad days," usually after visiting her company's manufacturing plant. She says she knows that her disease is mild, so she doesn't see a need to change anything and asks for a refill of her SABA inhaler. Her disease control, as reflected by current symptom impairment and risk from prior-year exacerbation history, is assessed with the Asthma Impairment and Risk Questionnaire (AIRQ [www.airqscore.com])[10,11] and she scores a 2 (not well controlled).

This patient is at risk for severe exacerbations and adverse asthma outcomes, even though her symptoms do not occur often. She has several factors that increase her risk of worse outcomes, including the use of SABA-only rescue therapy with no anti-inflammatory treatment, an AIRQ score of 2, and previous need for SCS.[12,13] She has received 3 courses of SCS for 3 exacerbations in the past 5 years, which represents a cumulative SCS exposure that increases her risk of steroid-associated adverse effects.[10,14] The patient's perspective of her disease seems to indicate a lack of understanding that she is at risk for severe exacerbations. The PCP should consider discussing an asthma action plan to educate the patient about the risks of SABA-only therapy, and the need for and benefits of ICS inclusion in her rescue treatment.[12]

DISEASE BURDEN OF MILD ASTHMA

Although most patients with asthma may be considered to have "mild" disease, less emphasis has historically been placed on disease burden for this population.[7,15] In recent years, multiple studies have demonstrated the significant disease burden of mild asthma, which is often in contrast to common perspectives of clinicians and patients.[7,15,16] Mild asthma is the most common form of asthma and can lead to severe exacerbations—up to 40% of exacerbations requiring emergency care are patients with mild asthma.[17] Additionally, 15% to 20% of fatal asthma attacks occur in patients reporting symptoms less than weekly or only with exertion in the previous 3 months.[18]

A high proportion of patients with mild asthma (50% to 65%) experience exacerbation events, and increasing SABA refills are associated with increases in total exacerbations and asthma-related costs of care.[8,19] Based on population-level data in the United States, about one-third of patients treated for mild-to-moderate asthma have claims for ≥2 SCS courses and/or ≥3 SABA refills per year.[6] This illustrates that a high proportion of those with mild or moderate asthma have uncontrolled disease.[4] Notably, in this US-based data, including approximately 4.5 million patients, 85.6% were treated for mild or moderate disease. Of the study population, 80.9% of all uncontrolled asthma observed was in patients presumed to have less severe disease.[6]

Regardless of the high burden of uncontrolled asthma in patients with less severe disease (ie, mild asthma), many patients with asthma have historically been and currently are prescribed SABA-only rescue therapy.[9,19] This results in a high burden of disease, risk of exacerbation, and risk of asthma-related mortality. An estimated 10% of patients with mild asthma transition to more severe disease over 10 years; older age at onset and inappropriate use of rescue medications are associated with higher likelihood of severe disease.[20]

While SCS can be used to treat asthma exacerbations, even occasional use of SCS leads to short- and long-term adverse effects from cumulative exposure. Adverse effects resulting from short-term (<30 day) SCS use include increases in risk of venous thromboembolism, fracture, and sepsis.[21] Higher lifetime cumulative doses of SCS (starting at 0.5 g of prednisone or equivalent, with a clear risk threshold of 1 g of prednisone or equivalent) may contribute to increases in cardiovascular disease, cerebrovascular disease, osteoporosis, pneumonia, type 2 diabetes, renal impairment, cataracts, weight gain, sleep apnea, anxiety, and depression.[14,22] In contrast, the addition of ICS to rescue therapy regimens is unlikely to be associated with the risks of systemic steroid exposure.[23]

ASSESSING AND DIAGNOSING MILD ASTHMA

Regardless of the lack of clarity in defining mild asthma, the heterogeneity of symptoms, the risk of adverse outcomes, and differing perspectives on the management of mild asthma, patients with less severe disease and/or occasional symptoms still need optimal, evidence-based care. Assessing and diagnosing patients with less severe disease can be particularly difficult due to these factors.[1,5]

Clinical diagnoses of asthma alone may be inadequate, highlighting the importance of spirometry in assessing and diagnosing asthma.[24] However, patients with less severe disease or occasional symptoms may not be experiencing symptoms when tests like spirometry are administered, which can result in normal results. Recently, the American Thoracic Society (ATS) produced updated guidance regarding the use of spirometry to diagnose asthma. Notably, spirometry does not need to demonstrate 12% reversibility for an asthma diagnosis, as previously recommended. Rather, bronchodilator responsiveness testing is recommended to determine whether there is any change in spirometric lung function

in response to bronchodilators.[25] A reasonable response (based on clinical judgment) to bronchodilators should still be observed to support an asthma diagnosis, in careful consideration with other clinical factors. Additionally, clinicians should be aware of and seek to minimize disparities in spirometry testing; specifically, members of minority groups (especially Black patients) are more likely to be underdiagnosed.[26-28] In addition to traditional spirometric criteria for asthma diagnosis (increase in forced expiratory volume in 1 second of ≥12% and ≥200 mL from baseline after bronchodilator administration), GINA now also recommends a trial of ICS treatment if there is a strong suspicion of asthma despite no evidence of variable airflow obstruction and other diagnoses are unlikely.[1]

Practical tips for accurately diagnosing mild asthma in primary care include:

- Complete a comprehensive history and physical examination
- Perform spirometry (note limitations as discussed above)
- Conduct additional testing as needed to rule out differential diagnoses
    - Fractional exhaled nitric oxide
    - Referral for exercise spirometry
    - Referral for methacholine or other challenge testing

Prioritizing the objective diagnosis of asthma will help to increase accuracy of the diagnosis and ensure patients receive appropriate treatment.

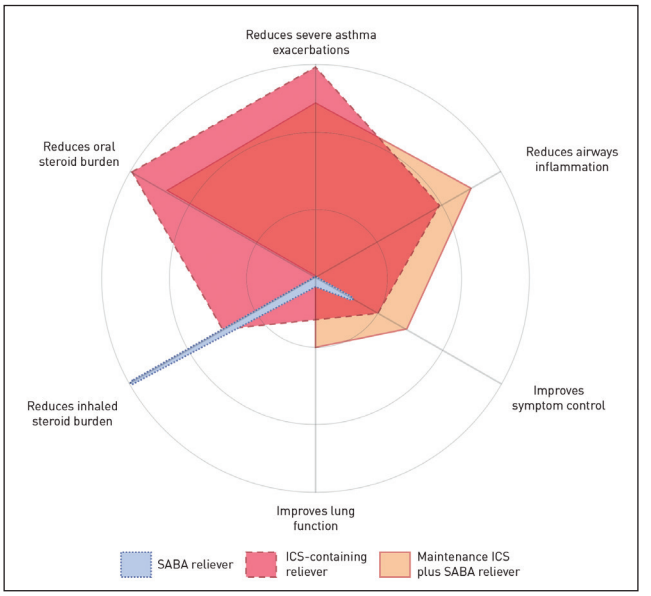
HOW TO TREAT MILD ASTHMA—ADOPTING THE NEW TREATMENT PARADIGM

With increasing evidence that SABA-only treatment is associated with worse asthma outcomes, new treatment paradigms for rescue therapy that include ICS are warranted, and these approaches are becoming widely recommended.[1,8] However, implementing this in clinical practice will require continued patient and clinician education. GINA has recommended against SABA-only rescue therapy in asthma for several years, and the European Respiratory Society guidelines also recommend against SABA-only rescue therapy.[1,29] The most recent (2020) NAEPP guidelines offer SABA-only rescue therapy as an option, although this recommendation was based on limited data available at the time.[3] NAEPP does offer an equal preference for as-needed concomitant ICS-SABA vs daily low-dose ICS with as-needed SABA as Step 2 treatment.[3] Additionally, recent studies have confirmed the risks of SABA-only rescue therapy and the benefits of adding ICS.[30,31] A conceptual comparison of the benefits of 3 treatment options for mild asthma highlights the limitations of SABA-only rescue therapy and supports the use of ICS-based regimens (**FIGURE 1**).[32]

Many patients (up to 70% with intermittent/mild-persistent asthma) in the United States refill SABA-only prescriptions without ICS.[33] Alternatives for clinicians and patients, according to product labeling, include the use of 2 separate inhalers (ICS and SABA) taken together for a rescue dose, or a SABA-ICS combination (albuterol-budesonide), which was approved by the US Food and Drug Administration (FDA) in 2023 for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma who are 18 years of age and older.[34] Prescribing SABA as a rescue option in the absence of concurrent use of a daily ICS inhaler for patients with intermittent or mild symptoms can be risky because these individuals are unlikely to be adherent to daily ICS.[33] Such patients are at increased exacerbation risk if SABA-only rescue therapy is all that they are using, especially when increasing airway inflammation is triggering symptoms and need for a rescue therapy.

The GINA report recommends including ICS in rescue regimens for patients with mild asthma, based on current evidence.[1] For patients with a new diagnosis of asthma who

FIGURE 1. Conceptual comparison of the relative benefits of 3 treatment regimens for asthma.[32]



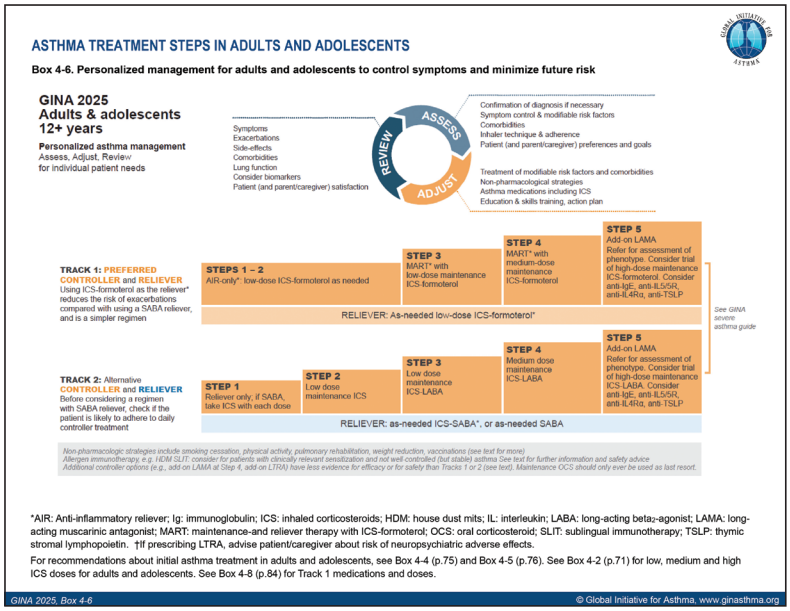
A conceptual comparison of the relative benefits of 3 treatment regimens for asthma: SABA reliever, combination ICS/fast-onset β_2-agonist reliever, and maintenance ICS plus SABA reliever.

While a SABA reliever may reduce inhaled steroid burden because it does not contain ICS, data show that lower use of ICS in asthma rescue therapy leads to adverse outcomes. While ICS-containing rescue/reliever therapy and maintenance ICS plus SABA rescue/reliever therapy have many overlapping benefits, ICS-containing rescue/reliever therapy exhibits the largest overall benefit of the 3 regimens shown in the figure, depicted by the largest area covered.

Source: Reproduced with permission of the © ERS 2025. O'Byrne PM, Reddel HK, Beasley R. The management of mild asthma. *Eur Respir J*. 2021;57:2003051. doi:10.1183/13993003.03051-2020

have symptoms on fewer than 3 to 5 days a week with normal or mildly reduced lung function, GINA recommends ICS + fast-acting bronchodilator (formoterol) as the preferred rescue/reliever therapy (**FIGURE 2**).[1] Notably, in the United States, no ICS-formoterol combination products are currently approved for as-needed use in rescue therapy. Based on current evidence and recommendations, no patient should be prescribed a SABA without also being prescribed an ICS. However, many patients are filling SABA prescriptions for asthma without an ICS, highlighting opportunities to better align current asthma practice with evidence. A discussion of potential adverse effects and out-of-pocket costs should also be considered to establish expectations, promote adherence, and encourage shared decision-making.[35]

FIGURE 2. GINA tracks 1 and 2: personalized asthma management for adults and adolescents to control symptoms and minimize future risk.[1]



Source: GINA ©2025 Global Initiative for Asthma, reprinted with permission. Available from www.ginasthma.org

Reducing exacerbations in mild asthma

Although exacerbations in patients with occasional symptoms or less severe disease can be difficult to predict, there could be up to a 10-day window of opportunity before an exacerbation peaks, where symptoms and SABA use increase. This window offers a chance for ICS intervention to prevent or reduce the severity of the exacerbation.[36] This can be achieved by patients increasing their maintenance ICS as part of an asthma action plan, or more simply by using a combined ICS-albuterol rescue inhaler.[37]

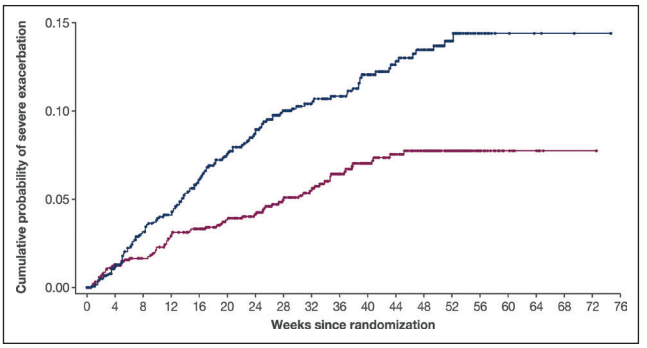
As patients get closer to exacerbation, there is increasing SABA use for both mild and moderate-to-severe disease.[36] Both groups have low use of maintenance therapy prior to an exacerbation but a marked increase in maintenance post-exacerbation, and both groups still have a proportion of patients with subsequent exacerbations (13% in mild and 27% in moderate-to-severe disease).[36] Additionally, a retrospective US study showed that patients treated for intermittent/mild-persistent asthma who receive SABA-only therapy have a greater occurrence of ≥1 severe exacerbation within a year vs those receiving low-dose ICS or a leukotriene modifier (61.2% vs 40.4% and 50.4%; P <.001 for both comparisons).[33] In those receiving SABA-only therapy, the proportions with ≥1 severe exacerbation were the highest, ranging from 52.5% to 70.4%.[33] In those receiving low-dose ICS, proportions with ≥1 severe exacerbation ranged from 36.0% to 44.9%. In those receiving a leukotriene modifier, proportions ranged from 47.3% to 54.7%. These ranges are based on the number of annual SABA fills.[33]

A recent study (BATURA) showed a significant reduction in exacerbations with albuterol-budesonide vs albuterol alone as rescue therapy in patients with mild asthma, highlighting the benefits of ICS-containing rescue therapy for exacerbation prevention.[12,13] BATURA examined the efficacy and safety of albuterol-budesonide 180/160 µg vs albuterol 180 µg in patients ≥12 years of age with mild asthma.[13] Patients were randomized 1:1 to albuterol-budesonide or albuterol alone as needed for symptoms for 12 to 52 weeks.[13] In the per protocol analysis, the albuterol-budesonide group experienced a statistically significant 47% reduction in the risk of a severe exacerbation vs those in the albuterol-only group (primary endpoint; hazard ratio, 0.53; 95% confidence interval: 0.39, 0.73; P <.001; **FIGURE 3**).[13] Secondary endpoints of BATURA showed a 53% reduction in annualized severe exacerbation rate and a 63% reduction in total SCS annualized dose in the albuterol-budesonide group vs the albuterol-only group (P <.001 for both comparisons).[13] Both treatment groups had generally comparable safety profiles.

CASE STUDY (CONTINUED)

The patient in the aforementioned case study is educated by her PCP about her considerable risk of severe exacerbations based on her clinical history and risk factors. Additionally, based on data from the recent BATURA study, continuing a SABA-only rescue therapy is likely to increase the risk of severe exacerbations and SCS use, compared to an ICS-containing rescue therapy.[13] With this understanding, she agrees to accept an ICS-containing rescue therapy in place of the SABA-only rescue therapy to reduce her risk of exacerbations. In this patient's case, ICS-containing

FIGURE 3. Primary endpoint of the BATURA study: time to first severe asthma exacerbation, per protocol analysis.[13]



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rescue therapy is preferred over ICS-containing maintenance therapy because the patient is likely to continue using the rescue inhaler at the expense of maintenance ICS.

SUMMARY

Mild asthma is often misperceived by clinicians and patients as conferring a low risk of asthma symptoms and severe exacerbations. However, recent evidence indicates that a significant proportion of patients with less severe asthma remain at high risk for exacerbations. Regardless of how severity is defined, there is rarely adequate rationale for SABA-alone rescue therapy in the absence of ICS for patients with asthma. ICS-containing rescue therapies reduce exacerbation risk compared to SABA-alone rescue regardless of the background daily maintenance regimen, including when added to daily maintenance ICS. Recognizing these risks and educating patients on the need for effective asthma regimens (ICS-containing maintenance and/or rescue regimens) can substantially reduce risk in patients with so-called mild asthma. ●

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Proactive Strategies for Mitigating Cardiopulmonary Risk in COPD

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KEY TAKEAWAYS

- Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) are often found in the same patients.
- Patients with COPD have an elevated risk of cardiovascular events, and COPD exacerbations further increase the risk.
- All patients with COPD should be evaluated for CVD while also considering multimorbid COPD in those with known CVD.
- Treatment for both conditions, including prevention and rapid treatment for COPD exacerbations, leads to improved outcomes and lower mortality rates.
- Proactive implementation of maintenance therapies in COPD to prevent exacerbations and reduce the risk of early death should be a goal of COPD management.
- Comanagement of COPD and CVD is imperative and often requires collaboration and effective communication across specialties. Primary care practitioners are especially important in treating patients and coordinating care for both conditions.
- Certain patient care approaches should be prescribed for COPD and CVD: smoking cessation and support, up-to-date adult immunization, activity or exercise support, and dietary guidance. COPD and CVD rehabilitation programs can provide this education and support for patients.

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INTRODUCTION

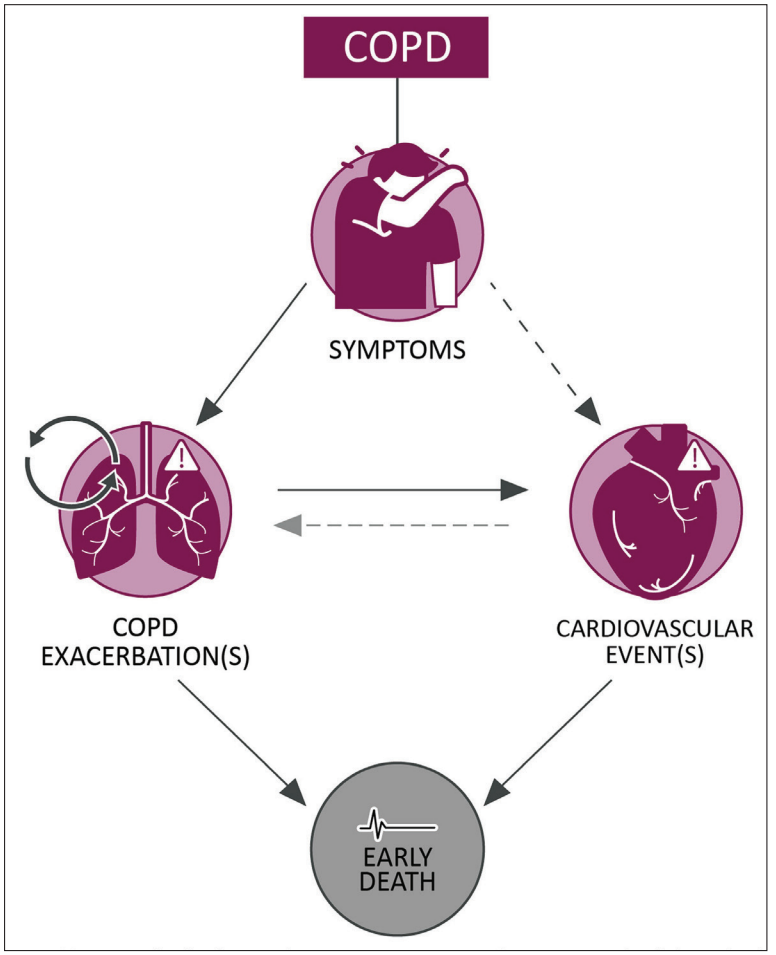
Chronic obstructive pulmonary disease (COPD) causes significant morbidity and mortality across the globe.[1,2] In the United States, COPD prevalence is estimated to be 4.3%, with 335,000 hospitalizations and 791,000 emergency department visits annually as of 2023.[1,3] COPD is often accompanied by cardiovascular disease (CVD) and COPD exacerbations, increasing the risk of both pulmonary and cardiovascular (CV) events (cardiopulmonary risk), and leading to potentially severe complications and/or early death (**FIGURE 1**).[4-7]

The association between COPD and CVD is becoming more widely recognized, and a new section in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025 report addresses CV risk in COPD.[8] These risks include exacerbations that may be associated with myocardial infarction, stroke, heart failure decompensation, arrhythmias, and death from any of these events.[7] Unmet needs in the diagnosis and clinical care of patients with multi-morbid COPD and CVD remain.

Inhaled therapies are the mainstay of COPD therapy, yet prescribing and use remain suboptimal. Despite the safety and efficacy of inhaled bronchodilator maintenance therapy, it remains underutilized in the United States, with only about 36% of patients receiving maintenance therapy.[9] Moreover, there is evidence of both undertreatment and overtreatment relative to disease severity.[10] Further, many patients with COPD continue to experience symptoms and exacerbations despite receiving maintenance therapy.[11] Alarmingly, prescribed treatment adherence tends to be low—ranging from 30% to 50% within a few months.[12] Decreased adherence is associated with worse COPD outcomes, including a higher risk for exacerbations and increased long-term mortality.[12] This was highlighted in a recent meta-analysis that showed a 40% increased risk of COPD exacerbations with poor adherence to inhaled medication.[13]

Although coexistence of COPD and CVD is common, clinicians may focus on only one of these diseases—ignoring the importance of diagnosing and treating both conditions simultaneously.[7,8] This may be due to the failure to consider that symptoms such as dyspnea are common in both, as are risk factors such as smoking. Even patients with clinically stable COPD (not having exacerbations) have an increased prevalence of CVDs such as hypertension, coronary artery disease, heart failure, and arrhythmias, which are prominent

FIGURE 1. COPD-associated cardiopulmonary risk.[7]



Abbreviation: COPD, chronic obstructive pulmonary disease.

Arrow type and shade indicate strength of association: strong association, with substantial supporting data (dark grey solid), emerging association, with some supporting data (dark grey dotted), suspected association, with data yet to be generated (light grey dotted).

Source: Singh D, et al. Implications of cardiopulmonary risk for the management of COPD: a narrative review. *Adv Ther*. 2024;41(6):2151-2167. No changes were made to the figure prior to reprinting. Figure licensed under a Creative Commons Attribution-NonCommercial 4.0 International License. The license can be viewed at this link: https://creativecommons.org/licenses/by-nc/4.0/legalcode

causes of death in individuals with COPD.[8] Assessing CV risk using tools such as the Framingham or QRisk score may underestimate CVD risk in patients with COPD.[8] GOLD recommends evaluating for the presence of major CVD in any patient with COPD and treating appropriately.[8]

CASE STUDY

Mary is a 57-year-old mother of 3 who works outside the home as an elementary school secretary. She presents to her primary care clinic for help with increasing shortness of breath and frequent productive cough. She was diagnosed with COPD (GOLD group B) 3 years ago and has been taking long-acting beta$_2$-agonist (LABA) + inhaled corticosteroid (ICS) therapy for the past 6 months after previously experiencing multiple exacerbations on LABA-only treatment. She is a former smoker (26-pack-year history) who stopped smoking at the time of her COPD diagnosis and remains off cigarettes. She has been treated for hypertension for 5 years with a diuretic. She has good inhaler technique and says she uses all her medications most days.

Currently she has taken on more work at school but finds she often feels too tired to get going in the morning and is short of breath halfway up the stairs at school. On questioning, she reports episodes of "being so tired I have nausea when trying to go upstairs quickly or hurry down the school halls."

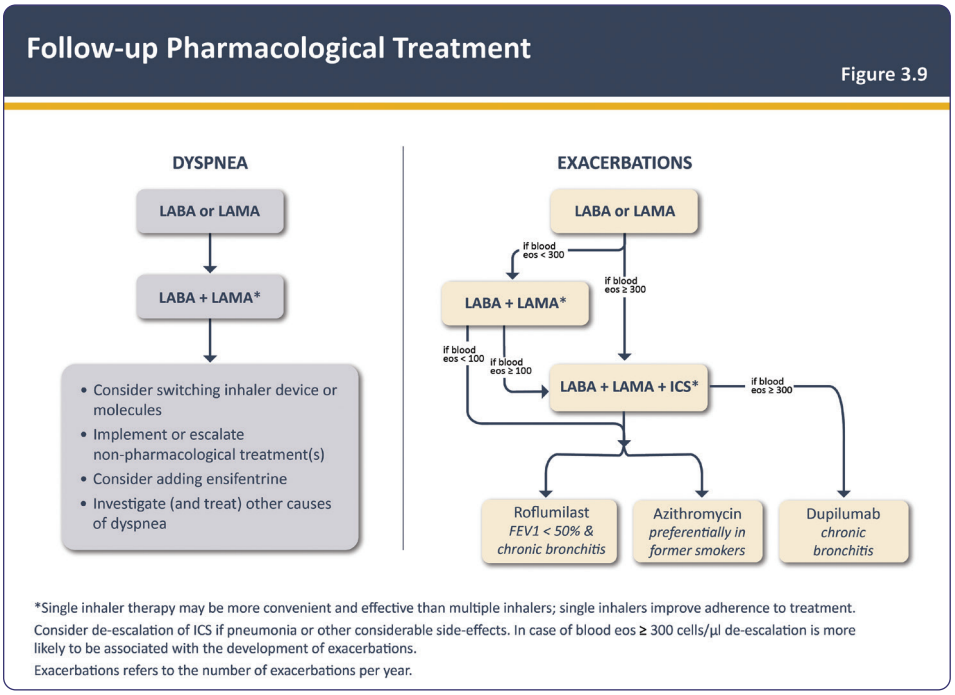
Clinical assessment: This patient is experiencing worsening dyspnea and frequent productive cough, but why? Questions for further investigation might include: Is her COPD progressing and causing more dyspnea? Are the increased dyspnea and perhaps the nausea variants of angina results of CVD that require evaluation and treatment?

COPD and CVD share several underlying mechanisms and risk factors such as hypoxemia, hyperinflation, systemic inflammation, age, smoking, physical inactivity, unhealthy diet, air pollution, genetics, and other health conditions such as diabetes, hypertension, hyperlipidemia, and infections.[14,15] These account for much of the multimorbidity of COPD and CVD and emphasize the need to evaluate individuals with COPD for CVD, as well as those with CVD for COPD. Patients with cardiopulmonary disease experience worse cardiac outcomes than those without. CV events are one of the most common causes of death in patients with COPD.[8,16,17] Assessment for CVD in those with known COPD is based on the patient's symptoms, personal risk factors, and available resources. These tests can vary from an electrocardiogram (ECG) and exercise-based stress test to imaging studies. Continued or repeated assessment of symptom levels may suggest additional or repeated evaluations over time. Additionally, patients with CVD and breathlessness should undergo spirometry to rule out COPD.

COPD-DRIVEN CARDIOPULMONARY RISK AND EXACERBATIONS

Although stable COPD is associated with multi morbid CVD, multiple dynamic and interacting pathophysiologic mecha-

FIGURE 2. GOLD 2025 escalation and de-escalation strategies for pharmacologic treatment for dyspnea and exacerbations.[8]



Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; LAMA, long-acting muscarinic antagonist.

nisms during and after a COPD exacerbation contribute to an increased risk of a range of cardiac events.[8,18] Major CV events are more likely after an acute COPD exacerbation, and CV risk can remain elevated for up to a year after a COPD exacerbation. Severe COPD exacerbations can double the risk of heart attack and increase risk of hospitalization and cardiopulmonary-related death.[19-24] Increased risk is related to worsening of systemic inflammation, abnormal pulmonary gas exchange, gas trapping, and lung hyperinflation.[8] In addition, reduced myocardial contractility (leading to pulmonary edema), pulmonary hypertension, and poor perfusion of systemic organs also worsen during COPD exacerbations.[8] This is highlighted in the results from the EXAcerbations of COPD and their OutcomeS in CardioVascular diseases (EXACOS-CV) study, a retrospective analysis of patients with newly diagnosed COPD.[25] In the US group studied, risk of death and CV events was highest within the first 30 days after an exacerbation and increased with subsequent exacerbations, remaining elevated for up to 2 years.[25]

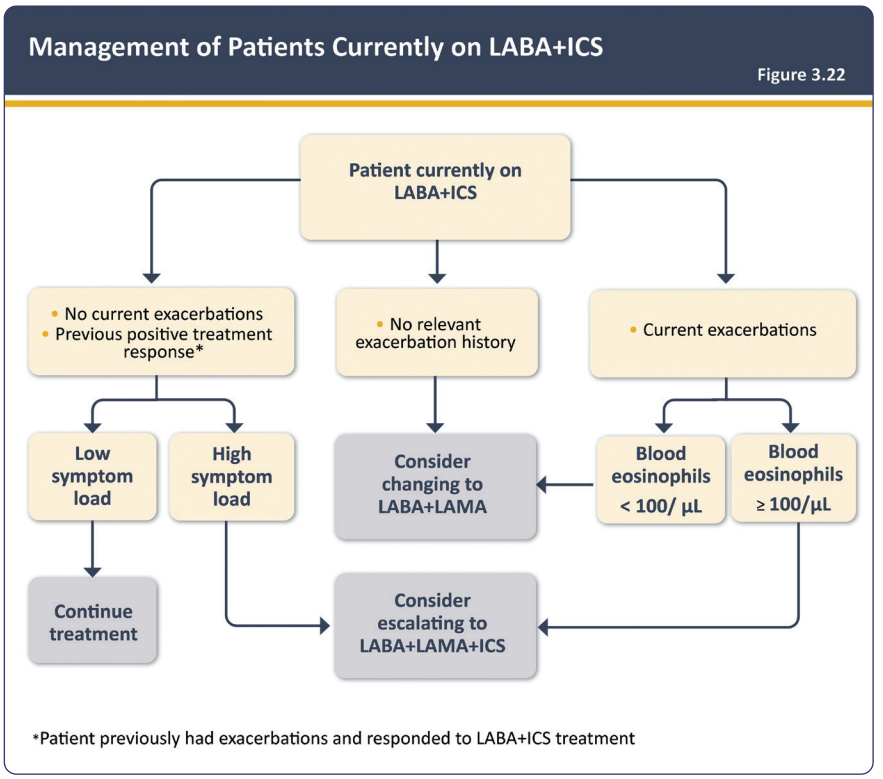
MANAGING COPD EXACERBATIONS AND CARDIOPULMONARY RISK

A COPD exacerbation is defined as "an event characterized by dyspnea and/or cough and sputum that worsen over <14 days" and is often associated with increased inflammation caused by airway infection, pollution, or other triggers.[8] Exacerbations are more common in some individuals with COPD, including those with poorer lung function and lower baseline oxygen saturations.[7] The goals for treating COPD exacerbations include minimizing the negative impact of the current event and preventing the development of future events.[8] For patients with persistent exacerbations on bronchodilator monotherapy, escalation to LABA + long-acting muscarinic antagonist [(LAMA) eosinophils <300 cells/µL] or LABA + LAMA + ICS (eosinophils ≥300 cells/µL) is recommended, and those with further exacerbations on LABA + LAMA therapy should be escalated to LABA + LAMA + ICS (**FIGURE 2**).[8] A beneficial response with ICS addition can be observed with blood eosinophils ≥100 cells/µL, with a greater magnitude of response expected with increasing eosinophil counts.[8]

Of note, some patients may be receiving LABA + ICS therapy, though this is not a recommended treatment for COPD.[8] If there is an indication for ICS use in COPD, LABA + LAMA + ICS has been demonstrated to be superior to LABA + ICS.[8] In such patients, clinicians should review relevant exacerbation history and adjust therapy to either LABA + LAMA + ICS or LABA + LAMA, depending on exacerbations and blood eosinophils (**FIGURE 3**).[8] Conversely, if there is no indication for ICS, patients receiving LABA + ICS should be switched to LABA + LAMA, which has been shown to be better than LABA monotherapy.[8]

Data from several trials suggest the benefit of triple therapy (LABA + LAMA + ICS), specifically for preventing COPD exacerbations in those at increased risk, leading to improvement in cardiopulmonary risk (**TABLE**).[26-32] Some studies indicate a reduction in cardiopulmonary events for patients receiving single-inhaler triple therapy.[27,33,34] Additional ongoing studies such as ATHLOS (NCT06067828) and THARROS (NCT06283966) are further evaluating the effects of triple therapy on cardiopulmonary outcomes in COPD. Real-world data suggest that prompt initiation of triple therapy within 30 days after a COPD exacerbation may

FIGURE 3. GOLD 2025 algorithm for adjusting therapy in patients with COPD currently receiving LABA + ICS.[8]



Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; LAMA, long-acting muscarinic antagonist.

further reduce the risk of future exacerbations compared with delayed intervention (>30 days).[35-37]

The GOLD 2025 report recommends proactive management of COPD exacerbations and cardiopulmonary risk, starting with appropriately identifying and treating COPD exacerbations, along with routine measurement of CV markers such as troponin and brain-natriuretic peptides during exacerbations when appropriate and possible.[8] Preventing COPD exacerbations and reducing cardiopulmonary risk through the use of effective therapies is critical to optimize patient outcomes.[8]

Guideline-directed cardiopulmonary therapies should be implemented at every opportunity; preventing exacerbations and intensively treating traditional CV risk factors should be a key focus in COPD management. Practical strategies for implementing effective treatments to address exacerbation and cardiopulmonary risk in COPD begin with the basics of smoking cessation and support, daily activity plans, dietary guidance, and completion of recommended adult immunizations for pneumococcal disease, COVID-19, pertussis, and herpes zoster.[8] COPD care will depend on history of exacerbations and oxygen status. An important and underused resource for both respiratory and CV support is COPD rehabilitation emphasizing education, activity, breathing exercises, medication adherence, and diet, which reduces the risk of repeat severe exacerbations.[38] As mentioned previously, dual bronchodilator therapy is the basis for all COPD management with the addition of ICS, roflumilast, and now biologic therapies when appropriate.[8]

Treatment for CVD depends on prior CVD history and current findings with select treatments for hypertension, cardiac failure, arrythmias, lipid abnormalities, and angina. These therapies are not contraindicated in individuals with COPD and in fact are central to the management of both CVD and COPD.[39]

CASE STUDY (CONTINUED)

Mary needs an updated evaluation of her COPD status, including pulse oximetry and spirometry or pulmonary function testing, to assess rapid progression of her COPD, which is causing greater dyspnea, worsening exacerbations, and possible CV events. Considering her previous positive response to ICS therapy, and based on exacerbation history, the patient would be a candidate for LABA + LAMA + ICS treatment.

In addition, her "nausea" with activity should be assessed as a potential angina variant. Considerations include an ECG and stress test. Like many people with COPD, Mary may not be a candidate for an exercise stress test, rather, requiring an imaging stress test. Such evaluations may include referral to a cardiologist, depending on the severity of symptoms, the primary care practitioner's comfort with ordering evaluations, and available local and health systems resources and guidance.

It is also appropriate to review her lipid profile and consider treating her abnormal lipids and blood pressure, updating her immunization status, and re-evaluating her inhaler technique.

Patients with COPD and CVD are often comanaged in primary care with specialty practitioners addressing more advanced therapies for COPD, CVD, and any other comorbidities such as diabetes, anxiety, or depression.

SUMMARY

COPD represents a substantial disease burden in the United States and is frequently associated with CVD, with cardio-

TABLE. Studies showing COPD exacerbation risk reduction with triple therapy (LAMA + LABA + ICS).

Study	Population	Treatment	Duration	Findings
ETHOS[27]	Moderate to very severe COPD and at least 1 exacerbation in the past year	Budesonide/ glycopyrrolate/ formoterol fumarate	52 weeks	Significant reduction in moderate or severe exacerbations vs LAMA + LABA and ICS + LABA
FULFIL[28]	Age ≥40 years, GOLD group D, and either ≥2 moderate COPD exacerbations or 1 severe COPD exacerbation within the past year	Fluticasone furoate/ umeclidinium/ vilanterol	24 weeks	Significant reduction in the rate of moderate or severe exacerbations vs ICS + LABA
IMPACT[26]	Age ≥40 years with symptomatic COPD and FEV_1 <50% predicted, ≥1 moderate or severe exacerbation in the past year, or FEV_1 50%-80% predicted and ≥2 moderate or ≥1 severe exacerbation in the past year	Fluticasone furoate/ umeclidinium/ vilanterol	52 weeks	Significant reduction in moderate or severe exacerbations vs LAMA + LABA and ICS + LABA
KRONOS[29]	Age 40-80 years, current or former smokers, and symptomatic for COPD despite receiving ≥2 inhaled maintenance therapies for ≥6 weeks	Budesonide/ glycopyrrolate/ formoterol fumarate	24 weeks	Significant reduction in the rate of moderate or severe exacerbations vs LAMA + LABA
TRILOGY[31] TRINITY[30] TRIBUTE[32]	TRILOGY and TRINITY: FEV_1 < 50%, ≥1 moderate-to-severe COPD exacerbation in the past year, and CAT score of ≥10 TRIBUTE: symptomatic COPD, severe or very severe airflow limitation, ≥1 moderate or severe exacerbation in the previous year, and receiving inhaled maintenance medication	Beclomethasone dipropionate/ glycopyrronium/ formoterol fumarate	52 weeks	Significant reduction in the rate of moderate or severe exacerbations compared to ICS + LABA, LAMA, or LAMA + LABA therapy

Abbreviations: CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; LAMA, long-acting muscarinic antagonist.

pulmonary risk increasing with exacerbations. Available and effective maintenance treatment often remains underused, putting many patients at continuing risk for symptoms, exacerbations, adverse outcomes, and comorbidities. Systemic inflammation, hyperinflation, and hypoxemia are associated with COPD and increase with exacerbation, resulting in sustained levels of greater respiratory and CV risk, even after the exacerbation resolves. Effective prevention and treatment of exacerbations, including timely optimization of therapies, are essential to mitigating cardiopulmonary risk in COPD. Multiple studies show reduction in the risk of exacerbations with triple therapy for appropriately selected patients. CVD assessment and targeted treatments should be pursued concomitantly to provide the greatest improvement in the patient's quality of life and outcomes. ●

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The Shifting Treatment Landscape for Alzheimer's Disease in Primary Care

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KEY TAKEAWAYS

- Alzheimer's disease (AD) is a common, progressive neurodegenerative disease that is frequently underdiagnosed and misdiagnosed.
- Delays in accurate diagnosis and management of AD can place an unnecessary burden on patients and their families.
- Primary care providers and primary care geriatricians are often the first to encounter patients with cognitive impairment, playing an essential role in the timely diagnosis and management of AD.
- Biomarker testing, which is increasingly available in care settings, can help reduce misdiagnosis of AD and determine eligibility for disease-modifying therapy.
- Treatment of AD is based on the stage of disease and may include amyloid-targeting therapies for patients with mild cognitive impairment or mild dementia due to AD.

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INTRODUCTION

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disease affecting cognition, behavior, and function, and its neuropathologic hallmarks are usually present decades before symptoms are evident.[1–3] AD is a highly prevalent disease in the United States (US) with a continually increasing healthcare challenge as the size of the aging population grows.[1] The population of Americans aged 65 years and older is projected to grow from 58 million in 2022 to 82 million in 2050, accompanied by a higher number and proportion of individuals with AD and other dementias, since the risk of dementia increases with advancing age.[1] Mortality rates are higher in people with AD, and AD is the fifth-leading cause of death for people in the US aged 65 years and older (2021 data).[1] Along with other dementias, AD has a high disease burden in the US, including effects on psychosocial aspects of patients' quality of life and significant direct and indirect costs, with an estimated $360 billion spent on healthcare and long-term care annually.[1]

AD progresses along a continuum that begins with preclinical AD, where neuropathologic changes are present without cognitive impairment, and progresses to a clinical presentation that includes mild cognitive impairment (MCI), mild dementia, and eventually moderate and severe dementia.[2] Several different staging systems describe the progression of AD, with variations in nomenclature but overall similarities with regard to pathophysiology and neurologic deficits.[2,4,5] Symptoms become evident in the MCI phase of the AD continuum, characterized by subtle cognitive and functional changes that may only be noticeable to the patient, family members, friends, and care partners.[1] AD pathology can be detected much earlier than symptoms and can establish the etiology of the symptoms. For example, amyloid plaque deposition can occur up to 20 years before the onset of cognitive symptoms.[4,6] Tau pathology may be detected in preclinical AD in the form of soluble P-tau protein, and neurofibrillary tangles (NFTs) may be detected with tau positron emission tomography (PET) closer to symptom onset. Both amyloid and tau are pathologic hallmarks of AD.[1,4,6] Despite the substantial and increasing burden of AD, the condition remains underdiagnosed in many clinical settings, including primary care.[1] Outside of research, a high proportion of patients who meet the diagnostic criteria for AD are not diagnosed. Per claims data, of those patients covered by Medicare with a diagnosis of AD or other dementia, only half of these patients reported that they were informed of their diagnosis by their clinician.[1] Misdiagnosis can result in potential harms, necessitating a change in approach to early evaluation and diagnosis of AD.[1]

The role of PCPs and geriatricians in AD care

The aging population and increase in older patients overall create an urgent need for better identification, management, and treatment of AD. Due to a shortage of AD specialists, it often falls to primary care providers (PCPs) to care for patients with MCI and AD.[1] Patients with early signs of dementia or AD often present first to their PCP or primary care geriatrician, who can help detect, diagnose, and manage MCI or mild dementia due to AD.[7] These providers serve a critical role in starting a timely assessment of MCI or mild dementia due to AD, initiating shared decision-making for referrals and treatment decisions, partnering in monitoring patients started on amyloid-targeting therapies (ATTs), and supporting patients and care partners throughout the care journey.

Patients and care partners often share their concerns for cognitive impairment with clinicians during routine and preventive care visits like the annual wellness visit (AWV), and clinicians and their staff may observe cognitive or behavioral changes during these visits. Prompt follow-up assessment is required.[7] However, non-dementia trained clinicians, and even AD specialists, may miss this critical opportunity to initiate investigation of this concern.[7,8] Clinicians may continue the AD work-up, ruling out other conditions or diseases, or they can refer the patient to AD specialists, such as dementia-trained neurologists, psychologists, or geriatricians.[2]

CASE STUDY

A 72-year-old woman with past medical history of hypothyroidism and hypertension controlled with medication presents to her primary care clinic with her husband, who voices concerns that she seems to be forgetting more and more things over the past year. She has missed paying utility bills and routine hair appointments. She is also experiencing agnosia, having trouble recalling names of familiar locations and objects.

The patient in this case scenario is experiencing cognitive impairment; therefore, MCI or mild dementia due to AD should be included in the differential diagnosis. Her PCP ordered basic labs to rule out potential underlying metabolic concerns (including B12 and thyroid-stimulating hormone). Rapid plasma reagin and human immunodeficiency virus (HIV) were not ordered due to the patient not having risk factors for neurosyphilis or HIV-associated dementia, respectively. The PCP reviewed and reconciled the patient's dosage and scheduling of medications and supplements to minimize iatrogenic effects on cognition using the Beer's list as a reference.[9] As patients age, the metabolism of medications may be impaired and medications may build up, potentiating toxic effects. The PCP also performed depression and hearing assessments during the routine exam, which were negative, and a validated cognitive assessment, which was positive for impairment. Finally, the PCP ordered magnetic resonance imaging (MRI) for structural evaluation of the brain to rule out potential acute non-AD factors.

WHO SHOULD BE EVALUATED FOR COGNITIVE IMPAIRMENT?

Historically, cognitive impairment testing has not been systemically initiated or addressed for all patient groups.[10] Detecting possible cognitive impairment in clinical settings can help identify patients who warrant further cognitive testing and evaluation.[11] The following individuals should be evaluated for cognitive impairment and potentially further AD testing[11]:

- Patients with memory concerns or other cognitive complaints, such as changes in personality, depression, unexplained worsening of chronic disease, and falls or balance issues
- Patients whose care partner or family reports cognitive impairment, with or without patient concurrence
- Medicare beneficiaries, as part of the AWV
  - The 3 billing codes for AWVs, which are built into many electronic medical record systems, are G0402, G0438, and G0439[12]
- Even though the United States Preventive Services Task Force has not provided guidance on cognitive assessments for adults aged 65 years and older, many geriatric-trained providers routinely assess all their patients annually or every 6 months

Despite cognitive assessment being a standard component of AWVs for patients with Medicare, only 16% of patients aged 65 years and older reported receiving a brief cognitive assessment regularly.[13] PCPs should consider routinely screening patients at risk for AD with one of several tools validated for use in primary care settings.[2] Five of the tools, each of various sensitivity, are described below; they are available online.

Mini-Mental State Examination (MMSE). The MMSE is a 30-item instrument administered to the patient, and it takes about 5-10 minutes to complete.[2,14] This tool is sensitive and reliable for detection of memory and language deficits but may not capture impaired executive functioning.[15]

Montreal Cognitive Assessment (MoCA). The MoCA is a 12-item assessment that takes about 10 minutes to complete.[2] This tool was originally developed to improve detection of MCI, and thus, it is more sensitive than the MMSE for evaluating visuospatial abilities, language, memory, and executive function.[15,16] Of note, clinicians are required to receive training and certification to administer the MoCA.

Mini Cognitive Assessment Instrument (Mini-Cog). This brief evaluation consists of a 3-item recall and clock drawing that is administered to the patient and takes about 2-3 min-

utes to complete.[2] This assessment requires no training, and the results are easy to interpret, though it may not capture very subtle changes.[2]

AD8 Dementia Screening Interview (AD8). This short, 2-to-3-minute, 8-item tool is usually administered to an informant to help detect dementia in patients based on the informant's responses.[2] Some experts suggest that the AD8 may be administered to patients in the absence of an informant with similar results, especially in patients with mild dementia.[17]

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). The IQCODE is another questionnaire designed to be administered to an informant, and it takes about 10 minutes to complete.[2,18]

Clinicians should be sensitive to patients who may have low health literacy and those who are affected by health disparities and other socioeconomic and psychosocial factors that may prevent access to testing or affect the process of evaluating cognitive impairment. If AD is suspected, the next step to support a diagnosis of AD is consideration and assessment of neuropathologic etiology.[1]

AD ETIOLOGY

AD is characterized by 2 underlying neuropathologic hallmarks: amyloid plaques and tau neurofibrillary tangles (NFTs). Extracellular beta-amyloid plaques and intracellular NFTs accumulate over time, leading to progressive neurodegeneration, synaptic dysfunction, and inflammation. Amyloid plaques form 10-20 years before symptom onset, whereas NFTs develop 5-10 years before cognitive symptoms.[1,2,4]

Historically, before progress in biomarkers, the diagnosis of AD was considered either clinical (using primarily clinical data) or neuropathologic (formulated post-mortem by visualizing corresponding neuropathologic changes). However, recent guidance supports the concept of a clinical-neuropathologic diagnosis.[3,5] Hence, an accurate diagnosis of AD requires both a clinical and biomarker evaluation, including detailed medical and social history (risk factors), patient symptoms, cognitive assessment, physical examination findings, laboratory testing, and possibly imaging to identify neuropathologic changes.[3]

The differential diagnosis in evaluating patients who present with symptoms suggestive of AD may be challenging, though AD is no longer diagnosed by symptomatology alone. Biomarker testing can help differentiate conditions that may have a clinical presentation like AD, especially with effects on cognition. Examples include other neurodegenerative diseases (such as Parkinson's disease or dementia due to vascular disease), insomnia, depression, excessive alcohol use, and use of certain medications. Nevertheless, AD is the most common cause of dementia, accounting for an estimated 60% to 80% of cases.[1] Vascular dementia accounts for 5% to 10% of cases, an estimated 5% of patients have dementia with Lewy bodies, and Parkinson's disease dementia accounts for about 3.6% of cases.[1] Additionally, frontotemporal degeneration accounts for about 10% of dementia cases in individuals younger than 65 years of age and about 3% of dementia cases in individuals 65 years of age and older.[1] More than 50% of patients with AD have mixed dementia, and by age 85, 85% of patients with any type of dementia will have a second type.[1]

Due to variable accessibility and specificity of testing, biomarker testing is often conducted after the patient has been referred to an AD specialist; testing may include amyloid PET, cerebrospinal fluid (CSF) analysis, and/or plasma analysis.[3] However, PCPs can order blood-based biomarker tests to help expedite the referral process and diagnosis if comfortable doing so.

Biomarkers in AD

Detection of AD neuropathology and associated neurodegenerative disease through structural imaging and fluid biomarkers has emerged as a key component of the diagnostic work-up.[2,3] The use of biomarker testing in AD can help address the high rates of misdiagnosis, as 25%-30% of patients with a clinical diagnosis of AD were misdiagnosed by dementia specialists. There are even higher rates of misdiagnosis in primary care.[19] Alongside PET imaging, CSF biomarkers and blood-based biomarker tests are options for evaluating cognitive impairment in older adults.[20,21]

Key biomarkers of AD pathology include amyloid beta peptide (Aβ) and phosphorylated tau (P-tau) protein, which are associated with amyloid plaques and neurofibrillary tangles. These biomarkers can be assessed through fluid-based testing (CSF or plasma) and imaging with amyloid PET (**TABLE 1**).[22] Commercially available biomarker tests include US Food and Drug Administration (FDA)-approved amyloid and tau PET. Recently, 3 in vitro CSF diagnostic tests have been authorized for use by the FDA. They are all hybrid ratios with strong concordance to amyloid PET.[23] Multiple plasma tests are commercially available as laboratory developed tests and report performance similar to FDA-cleared CSF assays (**BOX 1**).[22,24,25–30] In a recently FDA-cleared blood biomarker, the ratio of phosphorylated tau to amyloid in plasma is intended to aid in the identification of amyloid pathology in appropriate patients.[26] These tests are not used alone, but with the patients' history and clinical assessments in making an early symptomatic AD diagnosis.[22,27–30]

The accuracy, cost-effectiveness, and accessibility of blood-based biomarkers for AD pathology in AD research and clinical diagnosis have been assessed in multiple studies.[23,31,32] In a study evaluating the use of blood-based biomarkers in primary and secondary care, PCPs had a diagnos-

TABLE 1. Key biomarker tests used in the diagnosis of AD via fluid-based and imaging-based analysis.[22,26]

AD Pathology	CSF	Plasma	Imaging
Amyloid beta proteinopathy	-	-	Amyloid PET
Phosphorylated and secreted tau	-	p-tau217	-
Hybrid ratios	p-tau181/ Aβ 42, t-tau/ Aβ 42, Aβ 42/40	%p-tau217 p-tau217/ Aβ 42	-

Abbreviations: %p-tau217, P-tau217/non-phosphorylated tau217 ratio.

The intended use of these tests is in adult patients, 55 years and older, presenting with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.

BOX 1. Classification of laboratory tests.[24,25]

Laboratory Test	Description	Examples
In vitro diagnostic tests (IVDs)	Used to analyze human samples in local or office laboratories and cleared by the FDA for use	CSF biomarkers
Laboratory developed tests	A subset of IVDs where the samples must be sent to a centralized CLIA-certified laboratory for analysis. They do not need FDA approval for use	Plasma biomarkers

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments of 1988.

tic accuracy of 61% for identifying clinical AD after a standard clinical examination vs 91% with the addition of a blood-based biomarker to the diagnostic work-up.[23] This research clearly demonstrates that incorporating AD biomarkers into a clinical work-up improves the diagnostic accuracy for both primary care and dementia specialists. Variability in coverage of biomarker assessments, inclusive of imaging, CSF analysis, and plasma tests, is a limitation of these approaches in AD detection and diagnosis. The adoption of biomarker tests has historically been relatively low and slow due to challenges with availability, cost, reimbursement, and PCP confidence in interpretation. However, blood-based biomarkers are becoming increasingly available clinically.[33,34]

Genetic testing

Many genetic features affect the risk of AD-related dementia. Of those that increase the risk of AD, ApoE ε4 is known to have the most significant impact on developing late-onset AD dementia.[1] Each individual inherits 1 of 3 alleles of the ApoE gene from each parent— ε2, ε3, or ε4. ApoE ε2 is protective, and those who have the ε2 form of ApoE tend to have onset of AD later in life. ApoE ε3 is the most common isoform and is considered neutral.[35] However, the risk of AD is greater in those carrying the ε4 variant, with highest risk for ApoE ε4 homozygotes vs ApoE ε4 heterozygotes vs non-carriers. It is important to note that while risk is increased in those carrying either 1 or 2 copies of the ε4 allele, ApoE ε4 carriers are not guaranteed to develop AD.[1] ApoE testing is also recommended to assess risk for development of amyloid-related imaging abnormalities (ARIA) associated with ATT treatment, which is discussed in more detail later. Of note, PCPs can order ApoE testing for patients expected to start an ATT to facilitate a more informed discussion of benefit and risk. ApoE testing is not required to begin treatment with ATTs, but it is recommended.[36]

It is also known that a small number of people (1% or fewer of those with AD) develop earlier-onset disease because of mutations to 3 specific genes, including the amyloid precursor protein gene or the genes for the presenilin 1 or the presenilin 2 proteins. These genetic mutations of the amyloid protein are called dominantly inherited or autosomal dominant AD. There are additional genetic risk factors for developing AD, such as Down syndrome. Individuals living with Down syndrome develop AD earlier than the unaffected population.[1] Patients who undergo genetic testing should receive appropriate genetic counseling and guidance regarding accurate interpretation of results.

The next step in helping to establish a diagnosis of AD includes working up the differential diagnosis. PCPs and geriatricians may initiate an evaluation or may choose to defer the evaluation until the patient can see a dementia specialist, expanding the multidisciplinary team of providers. Referrals may occur at different points across the patient's journey among providers to establish a diagnosis. The decision to refer may be based on provider knowledge, availability of dementia specialists, time, and infrastructure of the practice environment or healthcare organization. Cognitive testing and laboratory assessment, including biomarker confirmation of AD neuropathology, are part of the evaluation. Moreover, connecting patients with suspected or confirmed MCI or mild dementia to a dementia specialist promotes a timely and accurate diagnosis of early symptomatic AD and sets the stage to discuss potential treatment options, including disease-modifying therapy.

What happens after a patient has been diagnosed with early symptomatic AD

Following a clinical and biomarker-supported diagnosis of AD, PCPs and geriatricians continue to play a key role in the continuity of care for patients diagnosed with AD and their care partners. PCPs and geriatricians can be involved in dis-

ease monitoring, education, and counseling, as they typically have more frequent touch points with patients than the dementia specialists. Patients often defer to their PCP and primary care geriatrician in complex disease management for support and understanding of subspecialist plans. Monitoring for worsening cognitive function should include cognitive and functional assessments at routine follow-up appointments about every 6-12 months, which can also occur in primary care.[2]

CURRENT APPROACHES TO TREATMENT OF AD

For patients managed in the primary care setting, PCPs can consider how best to disclose the diagnosis to the patient and care partners as well as discuss treatment options and support resources.[2,37] In the event that the patient is no longer able to make informed decisions for themselves, PCPs can encourage patients and care partners to have conversations about advanced care planning.[2] After a diagnosis of AD has been verified by a dementia specialist, treatment can be initiated based on disease stage, patient characteristics, and agreed-upon treatment and life goals for the patient. Additionally, for patients who have trouble coordinating medical visits, a telehealth appointment or the PCP consulting with the dementia specialist may be an option.

Nonpharmacologic therapy

Nonpharmacologic therapies can have a positive impact on the quality of life for patients with MCI and mild dementia due to AD and are relatively safe and inexpensive.[2,14] Possible nonpharmacologic interventions include dietary changes, physical exercise, cognitive training, social interactions with others, adequate sleep, music- and art-based therapies, and proper personal hygiene.[1,14,38] Often, nonpharmacologic therapies are used with the specific aim of reducing behavioral and psychological symptoms, such as depression, apathy, agitation, aggression, sleep disturbances, and wandering.[1] Connecting patients and families with community resources is a critical component of supportive care.

Pharmacologic therapy—symptomatic treatments

Three acetylcholinesterase inhibitors (AChE-I) for symptomatic treatment of AD are currently available for patients diagnosed with Alzheimer's dementia. These agents can provide symptomatic benefit but do not affect the underlying neuropathological changes associated with AD.[1,2,39] An N-methyl-D-aspartate (NMDA) receptor antagonist is also approved for use for moderate or severe AD.[39] A combination acetylcholinesterase inhibitor and an NMDA antagonist is also available.[1] Common side effects of these symptomatic therapies include headaches, nausea, and weight loss.[1] Please note, there are no approved medications with a labeled indication for treatment of MCI.

Pharmacologic therapy—ATTs

ATTs are monoclonal antibodies that can modify the underlying pathology of AD. In clinical trials, they have been shown to slow cognitive and functional decline in patients with MCI or mild dementia, due to early symptomatic AD with evidence of amyloid pathology by reducing amyloid beta plaques, the accumulation of which is a defining feature of AD.[1]

Adverse effects of ATTs include headaches, infusion-related reactions, and ARIA.[1] ARIA is a common side effect that is usually temporary and asymptomatic but can be serious and life-threatening in some cases. It can involve swelling and/or microhemorrhage in some areas of the brain. Patients with ARIA may present with symptoms that mimic an acute stroke, including focal neurologic weakness, dizziness, headache, confusion, nausea, gait difficulty, and vision changes. The term ARIA is inclusive of 2 types of findings on MRI: 1) ARIA-edema (ARIA-E), observed on MRI as vasogenic cerebral edema or sulcal effusion; 2) ARIA-hemosiderin deposition (ARIA-H), which includes microhemorrhage, macrohemorrhage, and superficial siderosis.[40] Managing ARIA may require discontinuing the ATT temporarily or indefinitely. It is recommended that patients undergo ApoE testing before starting treatment with ATTs due to the increased risk for ApoE ε4 carriers of developing ARIA.[1]

When a patient has been started on an ATT, the dementia specialist will monitor the duration of treatment. However, PCPs and non-ATT-prescribing geriatricians can assist with monitoring disease progression via the use of cognitive assessment tools. PCPs and non-ATT-prescribing geriatricians also have an important role in monitoring for potential side effects.[2] Establishing programs or initiatives that encourage collaboration between PCPs and AD specialists can support patients and care partners throughout the care journey.[7] Clear communication between the care team, patients, and care partners is essential for optimal outcomes. Enlisting staff such as patient navigators and social workers may help facilitate the communication and coordination among providers, patients, and their care partners.

CASE STUDY (CONTINUED)

The patient was referred to a dementia specialist. The next step was confirmation of amyloid pathology, which can be performed via PET imaging, CSF biomarker, or blood-based biomarker assessments. Based on the clinical and neuropathologic evidence, the patient was diagnosed with mild dementia due to AD. This diagnosis was shared with the patient, her care partner, and the patient's PCP.

After diagnosis disclosure, the patient, her care partner, and the dementia specialist discussed and considered treatment options. This discussion included consideration of ATTs that may slow the progression of early symptomatic AD.

SUMMARY

This article described the shifting treatment landscape for AD in primary care to provide patient-centered care, with the goal of optimizing patient outcomes. AD is a common, progressive disease that is frequently underdiagnosed and misdiagnosed, resulting in delays in appropriate symptom and disease management. PCPs and geriatricians are often the first to encounter patients with signs and symptoms of cognitive impairment and are critical to a timely and accurate diagnosis and urgent management of AD. The use of biomarker testing, which is becoming increasingly available in more care settings, can help reduce misdiagnosis of AD and determine eligibility for disease-modifying therapy. Treatment of AD is based on the clinical stage of disease and evidence of amyloid neuropathology. The use of biomarker testing may augment the ability to help patients earlier in the symptomatic stages and provide the opportunity for treatment. Treatment of MCI and mild dementia due to AD with evidence of amyloid pathology may involve ATTs. Understanding the shifting paradigm may aid PCPs and geriatricians in managing their patients living with MCI and mild dementia due to AD. ●

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What's New and Around the Corner in CGM?

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Describe new and emerging technologies in continuous glucose monitoring (CGM) use, including over-the-counter (OTC) CGM devices and continuous glucose-ketone monitoring.
- Interpret CGM data, such as the ambulatory glucose profile (AGP) accurately to inform changes in diabetes therapy and optimize glucose control.
- Initiate CGM in patients with diabetes who would benefit from enhanced glucose monitoring and better blood glucose control, including those with insulin delivery devices.
- Engage members of the health care team in collaborating on diabetes management to facilitate patients acquiring CGM devices.

KEY TAKEAWAYS

- The goal of therapy for glycemic control in diabetes is to reduce hyperglycemia without causing hypoglycemia.
- A lack of symptoms does not mean that patients are not experiencing dysglycemia.
- Glycated hemoglobin alone is an average glucose metric that is unable to reveal areas for therapeutic changes; self-glucose monitoring is limited as it only reveals a point-in-time metric and can be painful to obtain.
- The use of CGM allows for visualization of blood glucose patterns via the AGP, which can be understood by clinicians, patients, and caregivers.
- New and emerging CGM technologies include OTC CGM devices and continuous glucose-ketone monitoring devices.
- Clinicians should seek to involve members of the multidisciplinary healthcare team for optimal diabetes care, as appropriate.
- Consider expanding CGM use in adults with type 2 diabetes (T2D) treated with glucose-lowering medications other than insulin to achieve and maintain glycemic goals.

TARGET AUDIENCE

Clinicians who wish to gain increased knowledge and greater competency regarding primary care management of CGM.

FACULTY

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Dr. Miller serves as speaker and advisory board member of Abbott, Bayer, Boehringer Ingelheim, Eli Lilly, Embecta, Insulet, and Novo Nordisk, and as an advisory board member of Corcept and Dexcom.

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INTRODUCTION

Diabetes affects an estimated 38.4 million people in the United States, or 11.6% of the population.[1] The majority of the diabetes care burden falls to primary care practitioners (PCPs) as approximately 90% of diabetes care in the United States occurs in the primary care setting.[2,3] Progress in the understanding of diabetes pathophysiology and new treatments have advanced the care of patients with type 1 diabetes (T1D) and type 2 diabetes (T2D), yet many patients still do not achieve glycemic targets.[4] Furthermore, existing models of care are insufficient to provide optimal diabetes care. Diabetes care occurs continuously, with the majority conducted by patients and caregivers—between visits and outside of clinical encounters.[5]

Limitations of HbA1c and blood glucose monitoring

While it is helpful to monitor glycemic control in diabetes using intermittent approaches such as glycated hemoglobin (HbA1c) and fingerstick blood glucose monitoring, these modalities have significant limitations. The HbA1c provides a 30- to 90-day retrospective average of blood glucose data, but HbA1c alone may not be very helpful for patients to understand their diabetes control.[6] Fingerstick blood glucose monitoring only measures blood glucose at a single point in time.[7]

HbA1c has been considered the gold standard in monitoring of diabetes care, but it provides only an average of a patient's blood glucose history. HbA1c may underestimate or overestimate glucose control and does not indicate glycemic variability, including the extent or timing of hypoglycemia and hyperglycemia.[8,9] HbA1c values have limited utility for insulin dosing decisions and can be unreliable in patients with certain conditions such as hemolytic anemia, hemoglobinopathies, iron deficiency, or pregnancy.[8,9]

Metrics obtained from continuous CGM, such as time in range (TIR), which measures the proportion of time a patient's blood glucose is within a target range (typically 70 to 180 mg/dL), provide more actionable information than HbA1c alone and should be used to complement HbA1c.[10] Each 5% increase in TIR is clinically beneficial.[10] Equivalent HbA1c values do not translate to equivalent TIR (**FIGURE 1**).[10]

Utility of CGM for glycemic monitoring

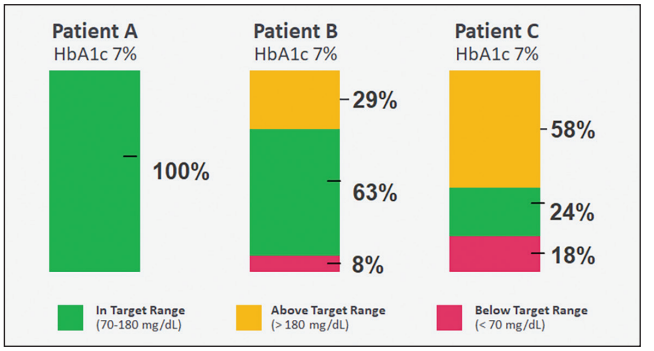
CGM allows clinicians and patients to move beyond traditional HbA1c and self-monitoring of blood glucose (SMBG) measurements, with access to more data obtained outside of the clinic, and more insights into patients' blood glucose patterns and detection of dysglycemia (**FIGURE 2**).

Diabetes technology such as CGM has improved overall care of patients with diabetes in recent years and has the potential to make a larger impact with optimal implementation in primary care settings.[11] The American Diabetes Association (ADA) and the American Association of Clinical Endocrinology recommend the use of CGM for many patients with diabetes and recognize the benefits of CGM use.[12,13] Specifically, the ADA *Standards of Care in Diabetes* recommend the following[12]:

- Diabetes devices should be offered to patients with diabetes.
- CGM should be offered to people with T1D early in the disease, even at the time of diagnosis.
- Recommend early initiation, including at diagnosis, of CGM depending on a person's or caregiver's needs and preferences.
- Real-time CGM or intermittently scanned CGM is recommended for diabetes management for people with diabetes receiving any insulin therapy.
- Consider using CGM in adults with T2D treated with glucose-lowering medications other than insulin to achieve and maintain glycemic goals.

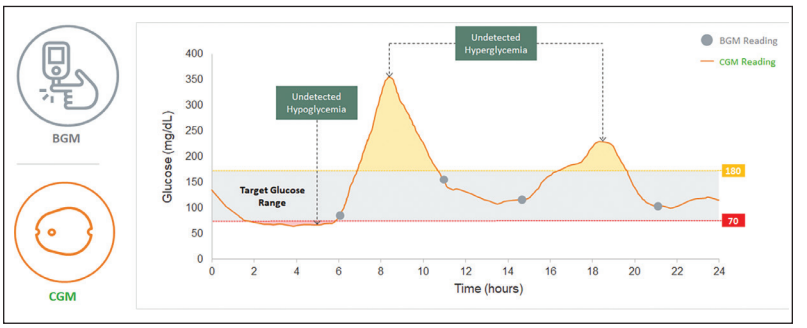
Furthermore, early use of CGM can support glycemic outcomes. Data indicate that CGM helps patients reach and maintain HbA1c targets in the first year of treatment and

FIGURE 1. Equal HbA1c values compared to different TIR values.[10]



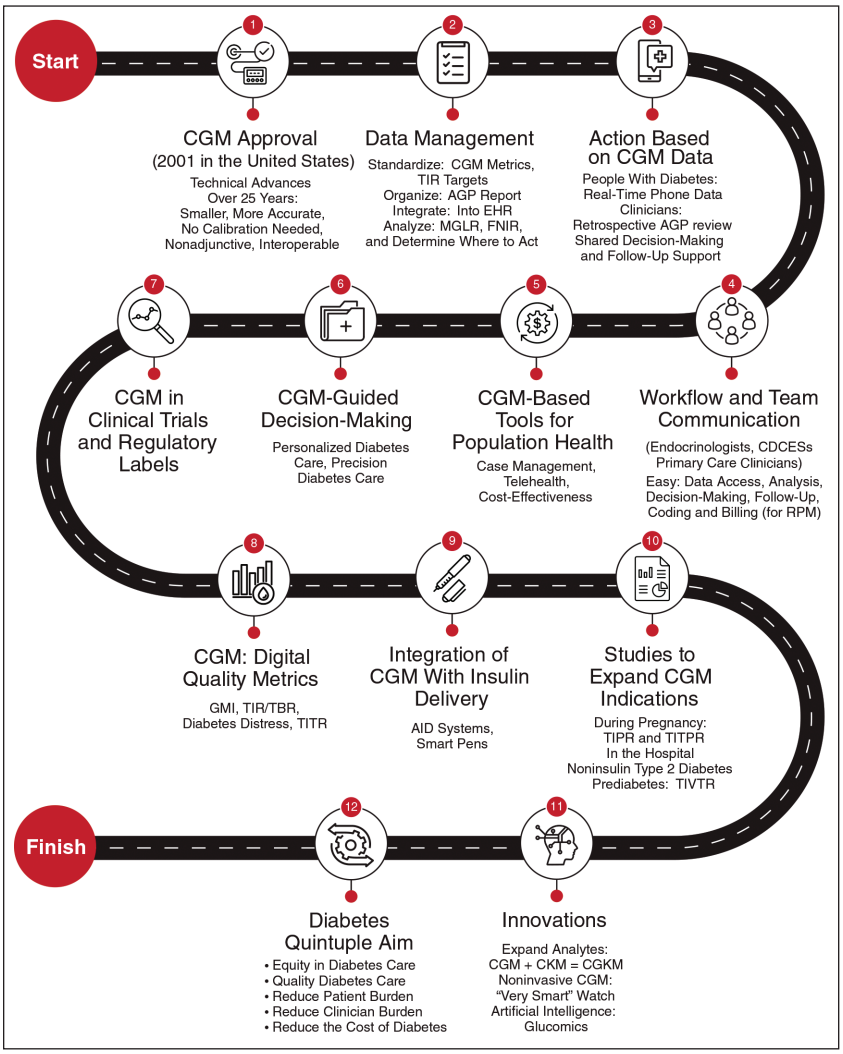
Abbreviations: HbA1c, glycated hemoglobin; TIR, time in range.
Not actual patient data; for illustrative purposes only.

FIGURE 2. Blood glucose monitoring vs CGM for detecting dysglycemia.



Abbreviations: BGM, blood glucose monitoring; CGM, continuous glucose monitoring.

FIGURE 3. Roadmap of the effective use of CGM: Innovation, investigation, and implementation.[15]



Abbreviations: AGP, ambulatory glucose profile; AID, automated insulin delivery; CDCES, Certified Diabetes Care and Education Specialist; CGM, continuous glucose monitoring; CGKM, continuous glucose-ketone monitoring; CKM, continuous ketone monitoring; EHR, electronic health record; FNIR, flat, narrow, in-range; GMI, glucose management indicator; MGLR, more green, less red; RPM, remote patient monitoring; TBR, time below range; TIPR; time in pregnancy range; TIR, time in range; TITPR, time in tight pregnancy range; TITR, time in tight range; TIVTR; time in very tight range.

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results in long-term health improvements, even when glycemic control wanes over time.[14] Patients with T2D who achieve glycemic targets soon after diagnosis are more likely to keep blood glucose within target range.[14] Additionally, managing glucose levels early in diabetes reduces the risk of complications.[14]

CASE STUDY

A 42-year-old woman presents to her primary care clinic for a follow-up appointment to discuss her T2D regimen. She states that she feels well today and has no complaints. Her HbA1c today is 7.5%, which is lower than it was 3 months ago (8%). She denies hypoglycemia and checks her blood glucose only when she does not feel well. She takes metformin 1000 mg twice daily and glipizide 10 mg twice daily, and she started dulaglutide 1.5 mg once weekly 2 months ago.

In this case study, the patient may appear to have satisfactory, and improving, glycemic control and may need only minor medication adjustments. However, more information is needed to obtain the full clinical picture of this patient's blood glucose patterns.

NEW AND EMERGING TECHNOLOGIES IN CGM

CGM technologies began with the first CGM device approval in the United States in 1999 and have continued to evolve over the past few decades (**FIGURE 3**).[15,16] Notable recent advances in CGM include the emergence of over-the-counter (OTC) CGM devices, continuous glucose-ketone monitoring, and artificial intelligence biosensors for CGM.

OTC CGM devices

Three OTC CGM devices are currently approved: Libre Rio, Stelo Glucose Biosensor, and Libre Lingo (**TABLE**).[17-19] The Libre Rio is an OTC CGM device that is intended for adults ≥18 years who manage diabetes through lifestyle modifications and noninsulin antihyperglycemic therapy.[17] The Stelo Glucose Biosensor is an OTC device designed for adults with prediabetes or T2D who are not taking insulin and do not experience problematic hypoglycemia.[18] The Lingo OTC CGM is designed for adults to better understand and improve general health and wellness.[19] It tracks glucose and provides personalized insights to help create healthy habits and improve overall well-being.

Continuous glucose-ketone monitoring

Diabetic ketoacidosis (DKA) is a serious complication of diabetes that can occur in patients with T1D (25% to 40%) or T2D (up to 34%).[20] It is characterized by the triad of hyperglycemia, ketosis, and anion gap metabolic acidosis, with manifestations of ketones in the blood and a sweet smell on the breath.[20] Patients taking a sodium-glucose cotransporter-2 inhibitor are at increased risk for DKA.[20]

TABLE. Characteristics of approved OTC CGM devices.[17-19]

	Libre Rio[17]	Stelo[18]	Libre Lingo[19]
Characteristic			
Wear period/ sensor duration	Up to 15 days	Up to 15 days + 12 hour grace period	Up to 14 days
Reading interval	1 minute	5 minutes	1 minute
Glucose range	40 to 400 mg/dL	70 to 250 mg/dL	55 to 200 mg/dL
Alarms	No	No	No
Finger sticks	No	No	No
Insurance coverage	No	No	No
Reader	No[a]	No[a]	No[a]

[a]Transmits data to a smartphone app.

Measuring ketones in the blood or urine at home can help detect ketosis, which can help identify those at risk for DKA early, prompting further evaluation and potential intervention. Currently, urine ketone strips and blood ketone strips and meters are available to measure ketones at home, and—when testing is conducted properly—both have similar accuracy.[21]

Integration of continuous ketone monitoring and CGM in the same sensor platform is an important consideration for streamlining measurement of ketones and glucose.[22] Integrated CGM-ketone sensors are actively being studied in clinical trials; 1 device has received US Food and Drug Administration breakthrough designation status and may become clinically available in the future.

Artificial intelligence biosensors for CGM

In recent years, the growing popularity of artificial intelligence (AI) in various applications has prompted efforts to improve the performance of CGM biosensors with AI, in addition to other applications of AI in diabetes, such as detection of retinopathy and macular edema.[16] The primary applications of leveraging AI to improve CGM biosensors include closed loop control algorithms, glucose predictions, and sensor calibration (**FIGURE 4**).[16] As AI and CGM technologies continue to advance, additional innovations in their capabilities are likely.

USING CGM IN PRACTICE: THE AGP AND ADJUSTING TREATMENT

The ambulatory glucose profile (AGP) report is the primary method of obtaining blood glucose data from a CGM device.[12] The AGP contains a summary of metrics, values, and goals to help clinicians and patients assess the overall quality of glucose management. Most AGP reports will display daily glucose profiles, as well as an aggregated glucose profile for the time period (often 14 days). The daily glucose profiles can be helpful in determining causes of patterns or exceptions to usual patterns. The aggregated glucose profile shows variability in the mean glucose and patterned areas of highs and lows, displaying all values as if collected over a single 24-hour period.[12]

Accurately interpreting the AGP report is essential to making treatment adjustments. Steps to quickly review and interpret CGM data from the AGP report might include the following:

1. "Riding the waves"
    a. Ask the patient to explain what patterns they see
    b. Identify occurrences of hypoglycemia (if any)
    c. Identify occurrences of hyperglycemia (if any)
    d. Identify any clear glucose patterns
2. "Peaks and valleys"
    a. Assess variability in glucose—more peaks and more valleys indicate greater glucose variability
3. "Compare with previous"
    a. Compare the AGP report with a previous report (if available) to identify similarities and differences

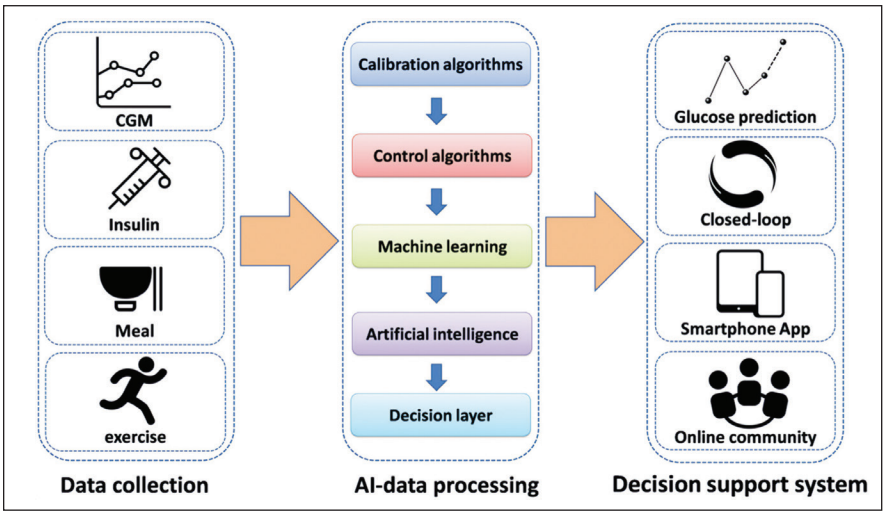
CASE STUDY (CONTINUED)

The patient started using a CGM device about 2 months ago, and her most recent data are shown in **FIGURE 5.** The AGP report indicates patterns of fasting hypoglycemia overnight and hyperglycemia in the late morning, afternoon, and evening. Her TIR is 58%, below her ideal TIR of >70%.[10] Time below range and time above range should also be reduced to <4% and <25%, respectively.[10] Obtaining additional information about the patient's dietary habits and providing counseling and careful medication adjustment would help improve this patient's TIR and reduce hypoglycemic and hyperglycemic episodes, resulting in better overall glycemic control.

IMPLEMENTING CGM IN PRIMARY CARE

While there are many benefits of using CGM, implementing this technology is not always straightforward. Benefits of CGM for patients with diabetes include improved health behav-

FIGURE 4. Representation of artificial intelligence applications in CGM.[16]



Abbreviations: AI, artificial intelligence; CGM, continuous glucose monitoring.

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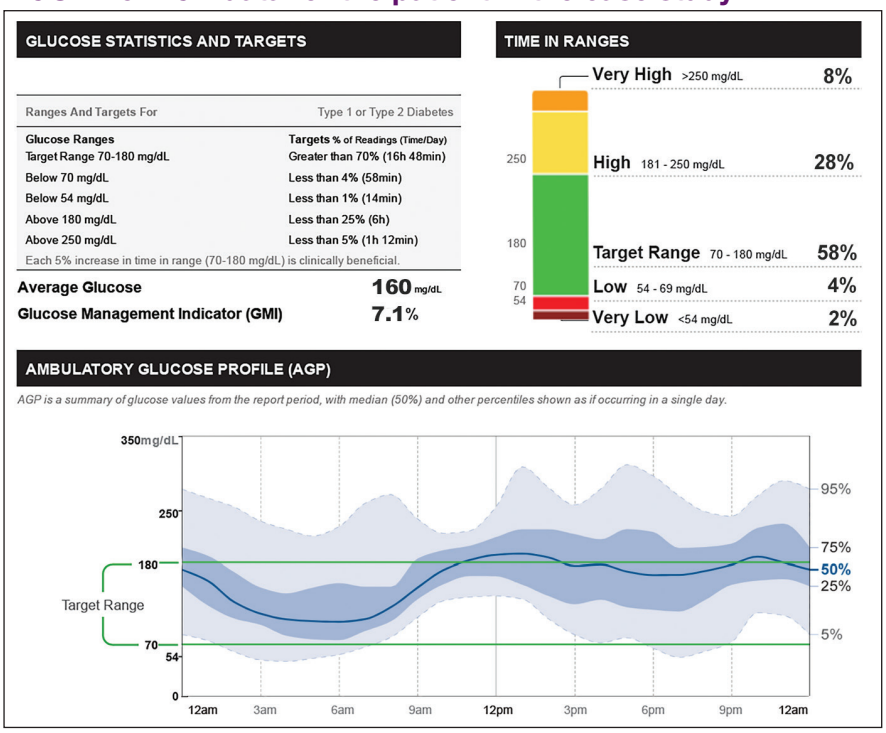
FIGURE 5. AGP data for the patient in the case study.



2-week range, time CGM active: 76%.

iors, reductions in HbA1c, less hypoglycemia, decreases in body weight, reduced caloric intake, increased physical activity, improved treatment satisfaction, and adherence to a personal eating plan.[11] For clinicians, CGM benefits include increased patient engagement, increased hypoglycemic awareness that can improve prevention, greater insight into therapeutic impacts on glucose management, and use of automated documentation to aid in data visualization.[23]

A primary barrier to CGM implementation is low rates of prescribing; one analysis using 2021 data estimated that only 13% of patients with T2D had used a CGM.[24] However, rates of CGM prescribing in primary care seem to be increasing.[24] Cost and insurance coverage can be additional barriers to CGM implementation, though coverage and reimbursement for CGM has improved in recent years. For example, the Centers for Medicare & Medicaid Services expanded coverage for CGM in 2023 to allow any patient using insulin to receive coverage for a CGM device.[25]

Employing appropriate coding and reimbursement strategies in clinics can help support clinic time spent on CGM implementation and monitoring. Coding for CGM may include the following[26]:

- 95249: personal CGM start-up and training
- 95250: professional CGM
- 95251: CGM interpretation
- 99212-99215: evaluation and management codes for patient encounters

Clinicians should also be sensitive to the potential effects of health disparities on CGM use and access, and should endeavor to involve the healthcare team in assisting with CGM access.[27,28] Indeed, CGM rates for patients in Federally Qualified Health Centers in the United States are estimated to be lower than the general population: 11% in patients with T1D and 1% in patients with T2D.[29] Health disparities that may affect CGM use include patients' location, socioeconomic status, racial and ethnic disparities, insurance coverage, technological challenges, and health literacy.[28] Involving other members of the care team such as diabetes educators, nutritionists, pharmacists, and nurses and offering

telehealth can improve patients' access to CGM and the overall quality of diabetes care.[30,31]

SUMMARY

PCPs play an increasingly important role in diabetes management in the United States, including in the use of diabetes technologies such as CGM. The use of CGM allows clinicians, patients, and caregivers to obtain more detailed information than what is available with HbA1c testing and traditional SMBG. CGM data visualization using the AGP helps mitigate the limitations of HbA1c and SMBG when evaluating a patient's overall glycemic control. New and emerging technologies in CGM include recently approved OTC CGM devices, the prospect of continuous glucose-ketone monitoring, and the use of AI in the CGM algorithm. As PCPs implement CGM in practice, with the involvement of other members of the healthcare team, patients are likely to have better access to CGM and improved glycemic control. ●

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