

Approach to the Identification and Differentiation of Migraine

Merle L. Diamond, MD; Susan Hutchinson, MD

CASE SCENARIO

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

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

Merle L. Diamond, MD, Director of Diamond Headache Clinic, Clinical Assistant Professor, Rosalind Franklin University of Medicine and Science, Chicago Medical School, Chicago, IL

Susan Hutchinson, MD, Director of Orange County Migraine & Headache Center, Irvine, CA

DISCLOSURES

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

Dr. Hutchinson discloses that she has served as a consultant and is on the advisory boards for Alder Biopharmaceuticals Inc.; Allergan plc; Amgen Inc.; Avanir Pharmaceuticals, Inc.; electroCore, LLC; Eli Lilly and Company; Supernus Pharmaceuticals, Inc.; and Teva Pharmaceutical Industries Ltd. She is on the speakers' bureaus for Allergan plc; Avanir Pharmaceuticals, Inc.; Pernix Therapeutics; and Supernus Pharmaceuticals, Inc. She has participated in research studies for GlaxoSmithKline plc.

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

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

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

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

CASE SCENARIO (CONT)

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

DIAGNOSIS

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

Differentiating secondary from primary headaches

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

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

Identifying the type of primary headache

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

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

FIGURE Ruling out secondary causes of headache: SNOOP4¹⁴

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

Figure: © Georg Thieme Verlag KG.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

COMMON QUESTIONS

Is there a quick way to diagnose migraine?

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

TABLE 3 ID Migraine Test²⁵

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

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

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

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

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

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

John E. Anderson, MD

ROLE OF INSULIN IN TYPE 1 AND TYPE 2 DIABETES MELLITUS

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

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

John E. Anderson, MD, Past President, The Frist Clinic, Nashville, Tennessee

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UNMET NEEDS WITH INJECTABLE INSULINS

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

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

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

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

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

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

ORALLY INHALED INSULIN

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

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

PHARMACOKINETICS/PHARMACODYNAMICS

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

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

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

EFFICACY OF AFREZZA INHALED INSULIN

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

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

TABLE 1 Efficacy of Afrezza

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

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

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

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

SAFETY OF TECHNOSPHERE INHALED INSULIN

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

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

TABLE 2 Safety of Afrezza

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

Abbreviations: FEV₁, forced expiratory volume in 1 second.

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

^bEvent requiring third-party assistance.

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

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

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

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

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

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

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

PATIENT SELECTION

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

TABLE 3 Patient education checklist

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

Abbreviations: FEV₁, forced expiratory volume in 1 second.

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

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

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

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

ADMINISTRATION AND DOSING CONSIDERATIONS

Administration

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

Dosing

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

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

PATIENT EDUCATION

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

CONCLUSIONS

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

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

Paul P. Doghramji, MD, FAAFP

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

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

TARGET AUDIENCE

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

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Paul P. Doghramji, MD, FAAFP, Family Physician, Collegeville Family Practice, Medical Director of Health Services, Ursinus College, Collegeville, Pennsylvania

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

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

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

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

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

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

DO ALL PATIENTS WITH HYPERURICEMIA DEVELOP GOUT?

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

CASE STUDY, STEVE:

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

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

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

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

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

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

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

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

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

CASE STUDY, STEVE (CONTINUED)

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

WHAT ARE THE OBJECTIVES OF LONG-TERM GOUT MANAGEMENT?

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

WHAT IS THE TARGET SUA GOAL?

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

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

HOW OFTEN SHOULD SUA BE MONITORED?

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

DOES LIFESTYLE MANAGEMENT HAVE A ROLE?

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

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

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

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

CASE STUDY, HARRIET:

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

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

WHAT ARE THE RECOMMENDATIONS AND EVIDENCE FOR EACH ULT?

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

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

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

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

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

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

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

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

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

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

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

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

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

Allopurinol

In patients with normal kidney function, allopurinol is initi-

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

Febuxostat

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

Probenecid

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

Lesinurad

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

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

Pegloticase

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

CASE STUDY, HARRIET (CONTINUED)

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

SUMMARY

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

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