

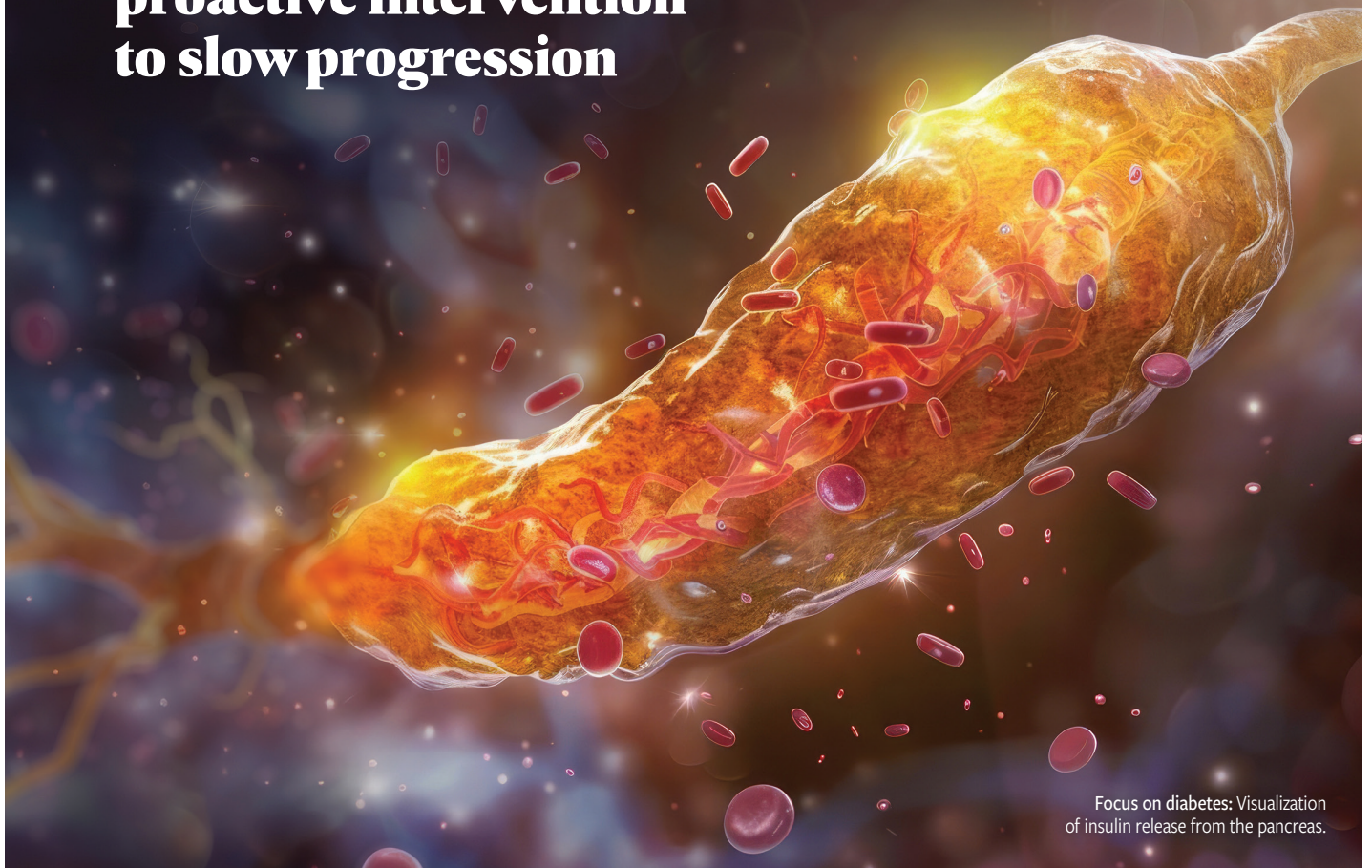
Patient Care[®]

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TYPE 1 DIABETES

Treatment options and proactive intervention to slow progression



Focus on diabetes: Visualization of insulin release from the pancreas.

Inside

VMS and Menopause
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Obstructive Sleep Apnea
Promoting Early Identification
and Timely Treatment

TAKING CHARGE EARLY:

Navigating Treatment Options to Delay T1D Progression

In this episode of the *Patient Care Frontline Insights* program, titled “Taking Charge Early: Navigating Treatment Options to Delay T1D Progression,” Javier Morales, MD, led a trio of diabetes management experts in a discussion of screening for type 1 diabetes (T1D) and navigating the staged progression of the disease, with an emphasis on avoiding diabetic ketoacidosis (DKA). They also discussed the landmark approval of teplizumab (Tziel), which is the first drug indicated to slow the progression of stage II to stage III T1D, or frank diabetes. The panelists also reviewed findings from the pivotal TrialNet 10 study (NCT01030861), which was the foundation for the FDA approval. The following transcript was edited for length and clarity.

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By **Grace Halsey** Senior Editor

Javier Morales, MD: I'd like to start with a brief overview of [T1D. I'll] ask Dr Molgaard to do that for us.

Aubrey Molgaard, DNP, ARNP, FNP-BC, CDCES: Certainly. Each year, approximately 64,000 Americans are diagnosed with [T1D], and that includes children and adults. Approximately 41% of cases are diagnosed in individuals younger than 20 years, with...59% occurring in those older than 20 years. Family history significantly increases risk, [as] first-degree relatives of individuals with [T1D] are 15 times more likely to develop the condition than the general population. The emotional toll [of] managing diabetes is significant, too; 36% of individuals report experiencing significant distress, and 63% express fear about complications affecting their well-being. The research shows that 28% find it challenging to stay positive about their condition. This emotional stress [also] affects family members and support systems.

We also know that [T1D] is associated with decreased life expectancy. A diagnosis in childhood can reduce longevity by 16 years and in adulthood by 10 years. The demands of management are daily and constant—monitoring blood glucose, managing insulin therapy, [and] watching diet and exercise. Patients also have to navigate the judgment tied to glucose readings. “I have a [glucose] sensor. It’s a great tool, but I’m always judged by that

number. It's a daily, minute-to-minute reflection of what I'm doing or how my control is." Economically, people with [T1D also] face 3 times higher direct medical costs.

Morales: How can we get involved with care for people with [T1D] early? Natalie, would you review recommendations from the American Diabetes Association [ADA] on screening for [T1D]?

Natalie Bellini, DNP, FNP-BC, BC-ADM, CDCES: Sure. Recently, the ADA has recognized the benefits of screening for [T1D] and identifying different stages based on the presence of specific autoantibodies. If we can detect the condition early, we can improve outcomes, and to start that means reducing the risk of DKA at diagnosis. DKA occurs in 40% to 60% of new [T1D] diagnoses in the US and can be life-threatening. The complete loss of β -cell function means no endogenous insulin [is] produced, so the body breaks down its own cells for energy, causing blood to become acidic. DKA leads to emergency [department] visits, prolonged hospital stays, and, in some cases, death. Screening for [T1D] can reduce the risk of DKA at diagnosis dramatically—to as low as 2% to 6%. In adults, antibody screening can help reclassify individuals who may have been misdiagnosed with type 2 diabetes but actually have type 1. Our textbook image of [T1D] is probably a 12-year-old who's lost weight, [whereas] type 2 is associated with an older person with obesity. [However], these stereotypes don't always hold. If an adult diagnosed with type 2 diabetes isn't responding to standard therapies, we need to screen for type 1.

Morales: Natalie, would you talk about the 3 stages of [T1D]? This will be] a [new] concept [for] many.

Bellini: Absolutely. Staging of [T1D] was first introduced in 2015. Before that, we thought of [T1D] as binary—you either had it or you didn't. At the time, the concept of

staging felt purely research based, with no treatment implications. Between the [National Institutes of Health (NIH)]-funded Diabetes Prevention Trial 1, which examined first-degree relatives of individuals with [T1D], and then the TrialNet program, we learned about the progression of [T1D] and identified 3 distinct stages.

In stage I, there are 2 or more autoantibodies present that signals the immune system has started to attack pancreatic β cells. Glucose levels are still normal, though, even after a glucose challenge, and no insulin is needed. The autoimmune attack continues in stage II, destroying more β cells and reducing insulin production, leading to dysglycemia. Glucose levels are abnormal but don't yet meet the diagnostic criteria for diabetes. Insulin still isn't needed because the remaining β cells can still compensate. [Here], dysglycemia mirrors what would fall under prediabetes or impaired fasting glucose in a textbook. Then we have stage III, which is what we traditionally think of as full-blown [T1D]. There are still 2 or more antibodies present, but the β cells are so damaged [that] they can no longer produce enough insulin, and the person develops hyperglycemia. We see classic symptoms, too: polyuria, polydipsia, polyphagia, fatigue, weakness, and unexplained weight loss.

Morales: What if someone has only 1 antibody?

Bellini: For patients with a single antibody, there's a 20% to 30% chance [that] they will develop a second antibody over time. Remember that 2 or more antibodies means a 100% lifetime risk for [T1D], regardless of when those antibodies are detected. That's why regularly monitoring this group is critical. Another complicating factor is that certain antibodies, [such as glutamic acid decarboxylase (GAD)]-specific antibodies, can appear with other autoimmune conditions, such as

Hashimoto or rheumatoid disease.

Morales: Natalie, would you discuss the benefits of delaying the progression of stage II to stage III?

Bellini: The shift from stage II to stage III can occur slowly for some people but suddenly for others. If we can intervene to slow that progression down, we may also be able to preserve some β -cell function. Any preserved function will enhance disease management. If we can slow progression, we can also reduce the risk of having DKA as the signal of the progression to stage III [T1D]. After DKA, long-term glucose control can be more volatile, and avoiding the condition can help smooth the transition into [T1D] management. Those who avoid DKA may initially need lower insulin doses and experience fewer complications.

In adult care, I've seen many 23-hour emergency admissions for DKA. Patients often don't even get a bed; they're in hallways or curtained-off areas in an overburdened emergency department. That is not a setting for fully explaining [T1D]. They get sent home with instructions like, "Take 10 units of Lantus and call your primary care provider." [That is] not the ideal start for [T1D] management. Screening lets us know that somebody is at risk for stage III [T1D], and we can be proactive with education while the disease is in stage II; we can talk about the disease, insulin therapy, [and] lifestyle change. The extra time lets us create more individualized plans.

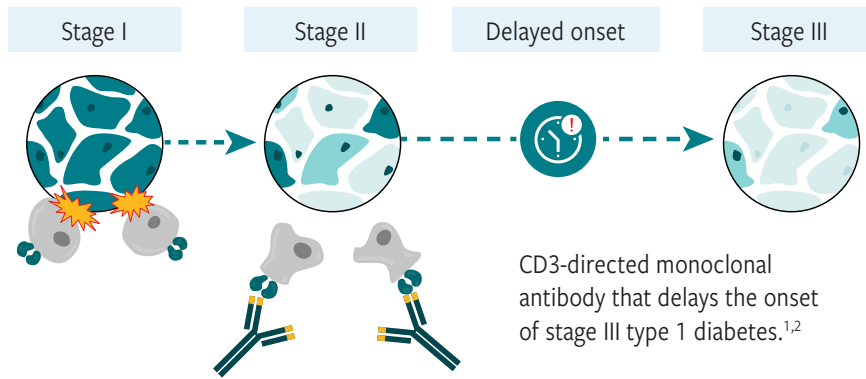
Abha Choudhary, MD: We follow [approximately] 2500 kids in our practice. We see 300 children every year with new onset [T1D], and almost half of them are in DKA. Some have to be admitted to the [intensive care unit]. They have [a] low pH, [an] altered mental status, [and] cerebral edema, [and] they need an insulin drip [and] IV [intravenous] fluids. Our 2 wards are full. We would do anything to decrease this rate.

FIGURE 1. Autoantibodies Preceding Type 1 Diabetes

Antibodies	Target
Insulin autoantibodies	Insulin-producing β cells
Glutamic acid decarboxylase autoantibodies (GADA)	GAD enzyme in β cells
Insulinoma-associated-2 autoantibodies (IA-2A)	IA-2A protein in β cells
Zinc transporter 8 autoantibodies (ZnT8A)	ZnT8 transporter β cells

FIGURE 2. Teplizumab: Mechanism of Action

Teplizumab is thought to modify disease progression from stage II to III T1D by preserving β -cell function.



1. FDA approves first drug that can delay onset of type 1 diabetes. News release; FDA. January 1, 2023. Accessed February 12, 2024. <https://www.fda.gov/media/164864/download>
2. Thakkar S, Chopra A, Nagendra L, Kalra S, Bhattacharya S. Teplizumab in type 1 diabetes mellitus: an updated review. *touchREV Endocrinol.* 2023;19(2):22-30. doi:10.17925/EE.2023.19.2.7

FIGURE 3. Median Time to Onset of Stage III T1D 2x Longer in Teplizumab-Treated vs Placebo-Treated Patients¹

~2-YEAR DELAY

Teplizumab **significantly delayed** stage III T1D onset compared with placebo in stage II T1D (~4 vs ~2 years median time to progression, teplizumab vs placebo, respectively).¹

~2.7-YEAR DELAY

Extended analysis further demonstrated a median time to stage III T1D diagnosis of 59.6 vs 27.1 months for teplizumab vs placebo, respectively.¹

Primary outcome: Change in β -cell function measured by stimulated C-peptide levels

Herold KC, Bundy BN, Long SA, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. *N Engl J Med.* 2019;381(7):603-613. doi:10.1056/NEJMoa1902226 T1D, type 1 diabetes.

Morales: Dr Choudhary, would you highlight the profile of who should be screened for [T1D] antibodies?

Choudhary: The general population has [a risk of approximately] 1 in 300 of developing [T1D], but for first-degree relatives, the risk is 15 times greater—approximately 1 in 20. The ADA and the International Society for Pediatric and Adolescent Diabetes both recommend screening first-degree relatives of individuals with [T1D]. We should also screen people with other autoimmune conditions, [such as] Hashimoto thyroiditis or celiac disease, because they have a 2- to 3-fold greater risk for [T1D]. There are specific [human leukocyte antigen] genotypes associated with [T1D], but testing for these is generally limited to research settings and isn't part of routine clinical practice. When to start screening is less definitive; there's no universal guidance yet. Some suggest screening at birth, [whereas] others recommend starting at age 2 years. The ADA has not issued firm recommendations, but the TrialNet program begins screening at [approximately] 2.5 years.

Morales: Natalie, what are the antibody types we should screen for, and how can we test for them?

Bellini: There are 5 antibodies that indicate this autoimmune condition [FIGURE 1], and [there are] several ways to test for them. In our office, we use Epic and have created an order set called "Type 1 Screen." It includes all relevant antibody tests bundled together, which can be sent to commercial labs, [such as] Quest or Labcorp. This makes it easy to order everything as a group. There are also research-based options,

[such as] TrialNet and ASK [Autoimmune Screening for Kids]. TrialNet is an NIH-funded study that screens first-degree relatives of people with [T1D] who are younger than 45 years. It involves either a finger stick with a free test kit that can be ordered or a blood draw at a TrialNet location. The initial test is for the 2 most common antibodies, and if either is positive, they'll test for the others. This is a low-cost option but has limitations. For example, if someone with only 1 antibody is missed, by the time they develop a second antibody and are retested, they may already have [T1D]. ASK is based in Colorado and is now open to both children and adults. It's free and, like TrialNet, uses a finger stick or blood draw. ASK also tests for celiac disease antibodies, which is good because [T1D] and celiac disease are often linked. ASK is available to anyone, not just first-degree relatives, making it more accessible for general population screening. Antibody panels can also be ordered online, typically costing \$100 to \$150. These panels test for markers such as GAD, [insulinoma associated-2 autoantibodies], and [insulin autoantibodies].

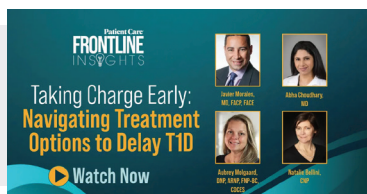
Morales: Now let's discuss intervention to delay stage III [T1D].

Choudhary: Teplizumab is a breakthrough as the first FDA-approved disease-modifying agent in endocrinology. It was approved in 2022 and [is] indicated for individuals with stage II [T1D] to delay progression to stage III by preserving β -cell function. [Teplizumab] is a monoclonal antibody targeting the CD3 molecule on T cells [FIGURE 2]. By binding to CD3, it modulates the immune response, essentially calming the immune system. The

pivotal phase 3 study that led to approval, published in *The New England Journal of Medicine*, was a multicenter, double-blind, randomized trial with 76 participants—first-degree relatives of patients with [T1D] in stage II. Participants were randomly assigned to receive either teplizumab or a placebo in a 14-day outpatient course. The median time to clinical diagnosis was 48.4 months in the teplizumab group vs 24.4 months in the placebo group—a delay of approximately 2 years [FIGURE 3]. In terms of adverse effects [AEs], the most common is lymphopenia, which is transient, peaking around day 4 [to] 5 and resolving within a few weeks on its own. Other [AEs] include mild rash, headache, and occasional neutropenia. Cytokine release syndrome, though rare, may present as fever, body aches, or headaches, which we manage effectively with premedications, [such as] antihistamines, antipyretics, antiemetics, and IV fluids. It took us [approximately] 18 months to set up our clinic to administer teplizumab therapy, but we have now developed a streamlined workflow and do infusions all week, including weekends.

Morales: Finally, which of our patients are eligible for teplizumab?

Bellini: Teplizumab is FDA approved for individuals 8 years and older [with] stage II [T1D]. It is a 30-minute infusion every day for 14 days, starting with a low dose that is doubled each day until day 5—and that is the maximum dose given from day 5 through 14. Of course, monitoring should take place during all infusions, and follow-up after the last one should continue to observe for potential [AEs] and follow blood glucose levels. ■



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PROACTIVE INTERVENTION:

Strategies for Slowing Type 1 Diabetes Progression

“Proactive intervention: Strategies for Slowing Type 1 Diabetes Progression,” is a *Patient Care Frontline Insights* program. In this episode, moderated by Javier Morales, MD, 3 diabetes management experts discuss the importance of screening for type 1 diabetes (T1D), the high-risk populations to include in screening, and monitoring the staged progression of the disease to avoid the development of diabetic ketoacidosis (DKA). The panel also discussed the landmark FDA approval of teplizumab, the first drug indicated to slow the progression from stage II to stage III T1D, or frank diabetes. The panelists also review findings from the pivotal TrialNet 10 study (NCT01030861), which was the foundation for the FDA approval. The following transcript was edited for length and clarity.

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By **Grace Halsey** Senior Editor

Javier Morales, MD: Dr Molgaard, would you provide background on the burden of [T1D] in the US?

Aubrey Molgaard, DNP, ARNP, FNP-BC, CDCES: [T1D] is diagnosed in both children and adults in the US, with 64,000 people diagnosed annually. Diagnosis is more common among adults aged 20 years and older at 59% than among those younger than 20 years [at] 41%. We know that family history increases the risk of [T1D] by 15-fold, so first-degree relatives have a higher risk than the general population. The emotional toll of the disease is significant, with 36% of people reporting diabetes distress; 63% say that the fear of developing diabetes-related complications affects their well-being, and 28% find it hard to remain positive [about] their condition. [T1D also] decreases life expectancy. A diagnosis in childhood may reduce lifespan by 16 years, and a diagnosis in an adult can reduce life expectancy by 10 years. There is also an economic toll; a person with [T1D] faces direct medical costs that are 3 times higher than people without the disorder.

Morales: Natalie, would you review the American Diabetes Association [ADA] recommendations for screening for [T1D]?

Natalie Bellini, DNP, FNP-BC, BC-ADM, CDCES: The ADA recommendations emphasize that screening

combined with consistent monitoring and education about the signs and symptoms of [T1D] can help prevent individuals in the early stages from progressing to DKA, which is often when a diagnosis is first made. DKA occurs in 40% to 60% of new [T1D] diagnoses in the US, and it can be life-threatening. Screening can reduce that risk to as low as 2% to 6%. It also offers the chance to identify adults who have [T1D] and may have been misdiagnosed with type 2 diabetes. In fact, up to 40% of adults [older than] 30 [years] are misdiagnosed. The classic profile of a 12-year-old with unexplained weight loss and a very low [body mass index] for [T1D] and an adult with obesity or overweight for type 2 diabetes needs to be reexamined in terms of both age and body composition. We have to shift our perspective.

Morales: Would you talk about the 3 stages of [T1D] that screening can identify, and criteria for each?

Bellini: There are 5 antibodies we use to look for that autoimmune response that indicates β cells are being attacked [FIGURE 1A]. If the sample is positive for 2 or more antibodies, that individual has a 100% lifetime risk of developing [T1D] and is now said to be in stage I [T1D]. At this stage, though, glucose levels remain within the normal range, even after a glucose load, and the individual is asymptomatic. As the autoimmune attack progresses, we move into stage II [T1D], where more β cells have been destroyed and dysglycemia emerges, where glucose measures are slightly above normal but none meet the threshold for a diagnosis of [T1D]. Finally, the disease moves into stage III, or frank [T1D], where there is little—if any— β -cell activity remaining, and the body can't produce enough insulin to maintain normal glucose levels. The person has hyperglycemia, and we see the typical symptoms of untreated [T1D]—polyuria,

polydipsia, polyphagia, fatigue, dry mouth, and increased appetite paired with unexplained weight loss. This is when the danger of DKA is [the] highest.

Morales: What about the person with a single antibody present? How do we proceed?

Bellini: For someone with 1 positive antibody, there's [approximately] a 20% to 30% chance they'll develop a second antibody. We know that as soon as there are 2 antibodies, the lifetime risk of developing [T1D] is 100%. We need to monitor these people closely and base our surveillance on their specific risk factors. A person with a first-degree relative and an uncle with [T1D] or who has a family history of other autoimmune conditions [eg, celiac disease or Hashimoto thyroiditis] would need more careful monitoring.

Morales: What are the potential consequences when that progression from stage II to stage III [T1D] is undetected?

Bellini: [T1D] staging is still a relatively new concept for all of us. The staging system was first published in 2015, and we didn't have options for prevention or even data on reducing the risk for DKA [at the time. However], as we'll discuss, we can intervene at stage II. If we can identify stage II [T1D] early, we can create a "softer landing" for our patients. In other words, we can start to educate the patient and the family on the process of managing [T1D]—we have time compared [with] when a patient's first knowledge of [T1D] happens when they're in the emergency department for DKA. If we can slow the progression to stage III, we also have a chance to preserve some β -cell function, which is associated with more effective long-term glycemic control. We can [also] reduce the risk of DKA, which can worsen long-term glucose control outcomes.

Morales: Would you talk about how we should focus our screening?

Bellini: According to the ADA and

the International Society for Pediatric and Adolescent Diabetes, we should screen all first-degree relatives of anyone [with T1D], as well as people with a personal history of [an] autoimmune disease, [such as] thyroiditis, Hashimoto [disease], and Grave disease or celiac disease. Parents, siblings, [and] children of anyone with an autoimmune disease should be screened, too. We also need to be aware that [T1D] prevalence is increasing across racial and ethnic groups and is [currently] growing faster among Black and Hispanic populations than among non-Hispanic White individuals. When it comes to [the] timing of screening, children of individuals with [T1D] should be screened at specific intervals—between ages 2 and 3 [years], 5 and 6 [years], and 9 and 11 [years]—because the presence of autoimmune antibodies can fluctuate over time. We have to screen multiple times during childhood. For adults, anyone with a first-degree relative who is newly diagnosed with [T1D] should request antibody screening at their next primary care visit...regardless of age. As far as screening frequency is concerned, that will depend on an individual's risk factors. If a patient has a brother with [T1D], a cousin with Hashimoto disease, and an aunt who has celiac disease, I'd rescreen annually.

Morales: What are the specific antibodies we are testing for, and what tests are available?

Bellini: There are 5 antibodies we need to be looking for. In our practice, we use Epic and have created a DotPhrase called "screen T1" that pulls up those specific antibodies. In terms of tests [FIGURE 1B], we can order through commercial labs, and there are even billing codes now. The TrialNet program is a great option if lab costs are a concern. TrialNet provides free screening for first-degree relatives of people with [T1D], covering individuals aged 2 to 45 years. The test can be ordered

FIGURE 1A. Autoantibodies Preceding Type 1 Diabetes

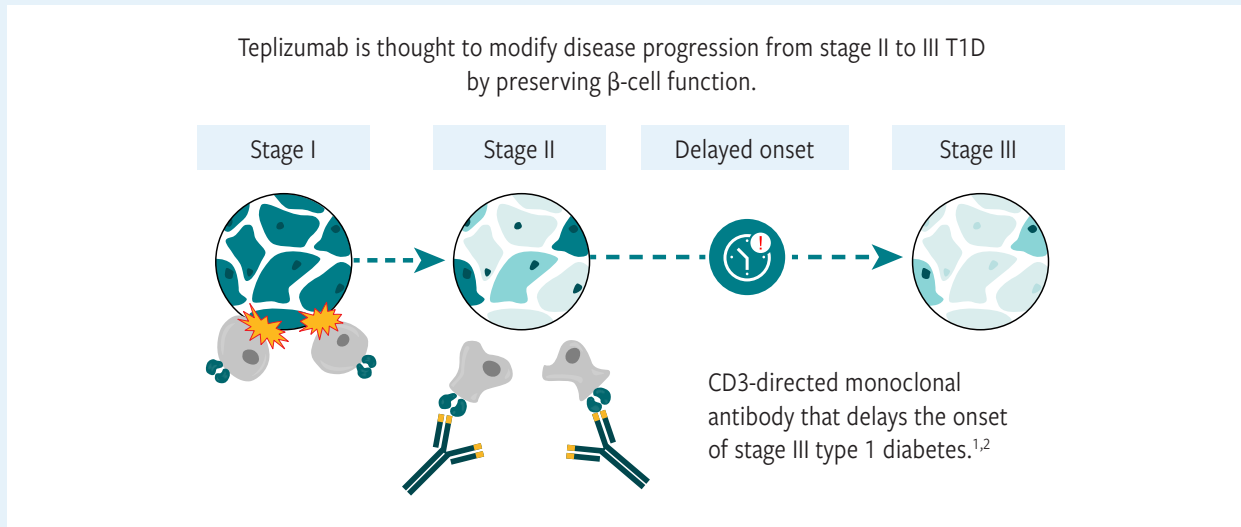
Insulin autoantibodies (IAA)
Glutamic acid decarboxylase autoantibodies (GADA)
Insulinoma-associated-2 autoantibodies (IA-2A)
Zinc transporter 8 autoantibodies (ZnT8A)
Islet cell autoantibodies (ICA)

FIGURE 1B. Types of Antibody Screening for Type 1 Diabetes*

	Tests	Screens for antibodies
Commercial labs	Blood draw	GADA, IA-2A, IAA, ICA, ZnT8A
TrialNet program	Blood draw or finger stick	GADA, IA-2A, IAA, ICA, ZnT8A*
Autoimmunity Screening for Kids	Blood draw or finger stick	GADA, IA-2A, IAA, ICA, ZnT8A
Online ordering	Finger stick	GADA, IA-2A, IAA

*Not an exhaustive list.

FIGURE 2. Teplizumab: Mechanism of Action



1. FDA approves first drug that can delay onset of type 1 diabetes. News release; FDA. January 1, 2023. Accessed February 12, 2024. <https://www.fda.gov/media/164864/download>
 2. Thakkar S, Chopra A, Nagendra L, Kalra S, Bhattacharya S. Teplizumab in type 1 diabetes mellitus: an updated review. *touchREV Endocrinol.* 2023;19(2):22-30. doi:10.17925/EE.2023.19.2.7

FIGURE 3. Infusion Site Options

Setting	Pros	Cons
Doctor's office	Supervised by provider	Limited scheduling flexibility
Infusion centers	Specialized staff & equipment	Travel required
At home with nurse	Convenience	Scheduling & lack of immediate medical assistance

online, and the kit is mailed to their home, or they can visit a participating lab or TrialNet site. The test initially screens for 2 antibodies; if either is positive, there will be follow-up testing for all 5. The ASK [Autoimmune Screening for Kids] program also includes adults now and is open to the general population without age restriction. Anyone can order a test kit, which screens for 4 antibodies [and] celiac disease—a common comorbidity with [T1D]. There are also online services that do antibody testing, typically for \$100.

Morales: Now we can talk about teplizumab, or Tzielid, which is the reason we have focused so keenly on screening for [T1D] in this session. Teplizumab was approved in November 2022 and is the first disease-modifying drug approved by the FDA for delaying [the] onset of [T1D] in at-risk patients. Dr Choudhary, would you explain how this medication works and the clinical trial behind the approval?

Abha Choudhary, MD: Teplizumab is an anti-CD3 monoclonal antibody that binds to the CD3 molecule on the surface of T cells where it increases regulatory T cells and modifies effector T cells, essentially interfering with T-cell activation [FIGURE 2]. We know [T1D] is an autoimmune process in which pancreatic β cells are attacked and destroyed. Teplizumab basically calms the immune system and delays the decline in the β -cell function.

The pivotal phase 3 study that was the basis for the FDA approval was a multicenter, double-blind randomized trial that enrolled 76 relatives of patients with [T1D]...in stage II...so, at least 2 autoantibodies and evidence of dysglycemia. The

participants were randomly assigned to a 14-day outpatient course of either teplizumab [n = 44] or placebo [n = 32]. The primary outcome showed a significant delay in the median time to [T1D] diagnosis: 48.4 months in the teplizumab group [vs] 24.4 months in the placebo group. Basically, teplizumab delayed the progression from stage II to stage III, or frank [T1D], by an average of 2 years in these high-risk individuals. This is what we are referring to when we say teplizumab offers a soft landing [for patients], because the delay translates [to] 2 years of more “normal” life, without insulin injections and blood glucose monitoring and with time to reduce anxiety about chronic disease management.

Regarding adverse effects, we found [that] the most common ones are minimal and manageable. Lymphopenia is seen most frequently and typically peaks at [approximately] day 4 or 5 of the infusion but resolves on its own within a few weeks. Rash is also common but transient. Although uncommon, elevations in liver enzymes have been observed, [which] is why we monitor hepatic function carefully during treatment. Cytokine release syndrome [CRS] is seen in [less] than 10% of patients, so it is rare, and we manage the symptoms that are typically flulike, such as joint pain, muscle aches, and general discomfort. There is a premedication protocol recommended during the first 5 infusions, including antipyretics, antiemetics, antihistamines, and normal saline boluses. It has been very effective for us. CRS can occur up to 28 days after infusion, so we tell patients to monitor symptoms and manage them with over-the-counter

medications as needed.

Morales: I want to move on to patient selection for teplizumab—Dr Choudhary?

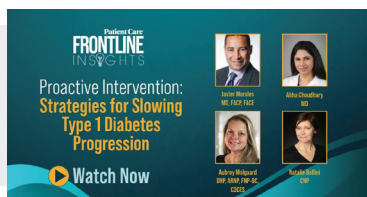
Choudhary: Teplizumab is indicated for individuals aged 8 years and older with a diagnosis of stage II [T1D]—again, at least 2 positive antibodies and proven dysglycemia. You [also] need to ensure that clinical history does not suggest type 2 diabetes. A note from my practice: When any pediatric patient comes in with new-onset diabetes, we check antibodies. Even if they look like type 2, we check pancreatic autoantibodies on everybody.

Morales: How do we use teplizumab? Aubrey, can you walk us through the infusion process?

Molgaard: The teplizumab infusion process is based on body surface area. The dosing starts on day 1 with 65 $\mu\text{g}/\text{m}^2$, increases to 125 $\mu\text{g}/\text{m}^2$ on day 2, 250 $\mu\text{g}/\text{m}^2$ on day 3, 500 $\mu\text{g}/\text{m}^2$ on day 4, and then reaches the maintenance dose of 1030 $\mu\text{g}/\text{m}^2$ from days 5 through 14. We talked about the prophylaxis protocol, and after the final infusion, you want to monitor the patient for up to 28 days for serious [adverse] effects and to observe blood glucose levels.

It's also important to coordinate care with the patient's other clinicians, including primary care physicians, pediatricians, endocrinologists, and pediatric endocrinologists. There are a few options for infusion setting, and each has pros and cons [FIGURE 3].

A hybrid approach is a great option. The patient completes the first 5 days at an outpatient center to ensure monitoring during titration. The remaining infusions are done at home. ■



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Click to watch the entire discussion on video.



VMS AND MENOPAUSE:

KNDy Neurons, NK Receptors, and Practical Insights

During a recent episode of *Patient Care Primary View*, titled “VMS and Menopause: KNDy Neurons, NK Receptors, and Practical Insights,” Mary Jane Minkin, MD, and Lisa Larkin, MD, discuss vasomotor symptoms (VMS) in menopause and a new class of nonhormonal therapies, including fezolinetant and elinzanetant. They also discuss kisspeptin/neurokinin B (NKB)/dynorphin (KNDy) neurons and their role in the development of VMS and highlight potential safety concerns and differences among neurokinin (NK) receptor antagonists. The following transcript was edited for length and clarity.

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By Sydney Jennings *Editor*

Minkin: First, can you discuss what KNDy neurons are?

Larkin: Before diving into KNDy neurons, I want to set the stage. For a long time, primary care physicians delegated menopause VMS back to obstetrician-gynecologists [OBGYNs], as they were thought to be solely about declining estrogen levels. We now understand that the pathophysiology of VMS goes much beyond estrogen. We know VMS [are]

related to a decline in estrogen and typically start in the perimenopause transition, but not all women develop hot flashes, even though 100% of women have declining estradiol levels [as they transition]. We now know that KNDy neurons in the hypothalamus play a significant role.

KNDy neurons project into the medial preoptic nucleus, [which is] the area housing the thermoregulatory center. When women develop VMS, their ability to regulate temperature diminishes. Slight changes in ambient temperature trigger these symptoms, which we now know are linked to KNDy neuron activity. During the menopause transition, declining estradiol levels cause these neurons to become hyperactive. This hyperactivity is driven by an imbalance in the binding of [NKB] molecules to receptors on KNDy neurons. This imbalance results in an overexpression of KNDy neurons and a narrowing of the thermoregulatory zone, which is experienced as a hot flash.

Minkin: You mentioned the role of estrogen in blocking [NKs]. Can you expand on this and explain the differences between [NK3] and [NK1] receptors?

Larkin: To start, there’s a balance between estrogen and [NK] signaling. In the absence of estrogen, KNDy neurons become hyperactive. Estrogen normally binds to receptors on these neurons, reducing their activity. Without estrogen, this regulation is lost. Different receptors on KNDy neurons have distinct roles. NK3 receptors are primarily associated with VMS, [whereas] NK1 receptors are believed to play a role in sleep. But again, it’s the balance between estrogen and the NKB molecule and the binding to these receptors that leads to the end organ effect. That’s where the exciting science is in terms of leading to targeted drug development.

Minkin: Medications are being developed to try to be a surrogate, in a sense, for estrogen. Can you tell us about the [NK] receptor antagonist currently available?

Larkin: Yes; fezolinetant is... an NK3 receptor antagonist that is FDA approved for the treatment of VMS caused by menopause. In the clinical trials that led to its approval, fezolinetant demonstrated significant improvement in VMS. [Before] its approval, there was only 1 FDA-approved medication for VMS—a selective serotonin reuptake inhibitor [SSRI]—and the other therapies we used in clinical practice were off-label. So, it's exciting to have targeted therapy available with clinical science behind it.

Minkin: Absolutely. It's worth noting that fezolinetant has a much stronger binding affinity for NK3 receptors compared [with] NK1 receptors—[approximately] 450 times stronger.

Switching gears, the hypothalamus also plays a crucial role in regulating sleep. Medications are currently being developed to address both VMS and sleep, which could be a game changer for many women experiencing menopause. Can you elaborate?

Larkin: Yes, with advances in understanding pathophysiology, we're seeing new generations of targeted therapies. [Although] VMS are important, many patients also struggle with sleep disruptions. For a long time, we thought sleep issues were secondary to VMS, but we now know that is not entirely correct. As you said, it's a "chicken or the egg" scenario.

Looking at the difference in receptors, the NK1 receptor is predominantly involved in sleep maintenance and sleep issues. One drug that is far along in the pipeline targets both the NK3 and NK1 receptors and has shown improvement in sleep in addition to VMS in clinical trials.

Minkin: The drug you are referring to is elinzanetant, which is currently being reviewed for FDA approval. Let's move on to practical insights for primary care physicians. How can we simplify the physiology of KNDy neurons and their role in VMS for our colleagues in primary care?

Larkin: It's not just estrogen, it's the loss of estrogen. But there is something else involved. It's really a balance of binding to these KNDy neurons with NKB and the interplay between estrogen and levels of NKB and binding that leads to the hot flash. To simplify it, an important set of neurons are controlling thermoregulation in the hypothalamus and targeted therapies are being developed.

Minkin: You just said it all, Lisa. Now, let's discuss fezolinetant, its clinical trials, and the [adverse] effects [AEs] we know about. It's officially not recommended for women with cirrhosis or severe liver disease due to concerns about liver involvement. There are some guidelines as far as regulation of use. It's recommended that women undergo baseline liver function tests—including AST [aspartate aminotransferase], ALT [alanine aminotransferase], and bilirubin—before starting therapy. AST and ALT levels must be less than twice the upper limit of normal before initiation.

In the trials, a small number of women developed liver function test abnormalities. This prompted recommendations for follow-up testing at 3, 6, and 9 months. Some women with elevated liver function tests discontinued the medication, [whereas] others continued and saw their levels return to normal.

However, in postmarketing studies, there was a report of 1 woman who developed cholestatic liver issues. She presented with clinical signs of jaundice and gastrointestinal symptoms, discontinued the

medication, and eventually recovered. This case raised concerns and led to updated monitoring recommendations. Lisa, as an internist, what are your thoughts?

Larkin: In the pivotal trials that led to fezolinetant's approval, liver function abnormalities were closely monitored, as is standard with new drug classes. Initially, the guidelines required baseline and periodic liver function tests, but the monitoring protocol has since been updated.

From my conversations with ob-gyn colleagues, the need for frequent monitoring was a concern when this medication launched. Unlike internists, ob-gyn's don't typically see patients every 3 months or monitor lab values routinely. For us, we're more comfortable with sequential liver function test monitoring.

The case you referenced, involving significant elevation in liver function tests and bilirubin, led to modifications in the package insert and updated monitoring guidelines. Now, liver function tests are recommended at baseline, monthly for 3 months, and then at 6 and 9 months. The patient in this case improved after discontinuing the medication, but this highlights the need for continued pharmacovigilance.

Minkin: One thing we're always concerned about, and our patients are appropriately concerned about, is whether there's any difference in the risk of malignancies between fezolinetant and elinzanetant. What do your findings suggest?

Larkin: First, I want to emphasize that neither fezolinetant nor elinzanetant are hormones; they are nonhormonal therapies. However, the FDA required endometrial safety monitoring for both, reflecting a standard practice established for managing VMS with hormone therapy.

In the trials of fezolinetant, there was [noted] concern for

endometrial hyperplasia and endometrial cancer, but it was minimal. So far, we haven't seen similar findings in the elinzanetant data. That said, I wouldn't consider these findings to exceed the normal rates of endometrial hyperplasia or cancer expected in the general population. It's important to remember that these issues naturally occur in aging women, and the monitoring requirements are precautionary.

Minkin: There's often a misconception that anything related to female organs must involve estrogen. We're showing that it is not; it's not a direct estrogen effect.

Larkin: I agree. And...elinzanetant hasn't been approved yet, and fezolinetant has only been available for [approximately] 18 months. We need to contextualize these concerns appropriately. I wouldn't overstate the risks of endometrial hyperplasia or cancer with either medication at this stage.

Minkin: I'd like to highlight the potential for these drugs to be adopted more widely—not just by OBGYNs but also by primary care physicians and internal medicine physicians. One common concern among primary care practitioners is vaginal bleeding, which often makes them hesitant to prescribe certain therapies. Fortunately, with this class of medications, vaginal bleeding isn't an issue.

Larkin: Absolutely, but I'd like to add another perspective. [Although] some primary care colleagues are excited about these drugs because they don't involve hormones, I've heard a troubling narrative. Some see these medications [as] completely [replacing] hormone therapy. That's a

misconception that concerns me. Menopausal hormone therapy remains the gold standard for many patients.

Minkin: For women who cannot or choose not to take estrogen therapy, there are alternatives available. Some of these options include medications traditionally used off-label for managing hot flashes. For instance, low-dose antidepressants—including SSRIs and [serotonin-norepinephrine reuptake inhibitors], gabapentin, and even certain bladder anticholinergics—have shown varying degrees of effectiveness.

However, these medications often come with [AEs] that can exacerbate existing menopausal symptoms. This is where a newer category of medications—NK3 and NK1 receptor antagonists—stands out; they are specifically effective for VMS and, importantly, do not come with the common [AEs] of older medications. Another remarkable attribute of these drugs is how quickly they work, [as] patients often notice improvement within 1 to 2 weeks. This rapid response can help sustain patient morale and [adherence], offering a welcomed alternative to traditional off-label treatments.

Larkin: I'd like to add to that by encouraging everyone to consult the 2023 [nonhormone] position statement from The Menopause Society. It provides an overview of both FDA-approved options for hot flashes—currently 2 medications, with a third, elinzanetant, pending approval—as well as off-label uses and nonpharmacological approaches, [such as] cognitive behavioral therapy, exercise, and

lifestyle changes.

[After the] Women's Health Initiative, we saw a significant shift away from hormone therapy. Many women turned to supplements and nonhormonal options, including SSRIs, which primary care providers often recommend for hot flashes. However, the data supporting these supplements [are] limited, and The Menopause Society ultimately does not recommend them due to a lack of robust evidence.

That said, many patients still want to try supplements, especially if they're pursuing a more natural approach. [Although] I generally don't oppose patients experimenting with supplements, I'm cautious when it comes to those with complex medical histories or who are on medications [such as] tamoxifen, aromatase inhibitors, or multiple blood pressure drugs. In such cases, potential drug interactions are a significant concern.

Minkin: What strategies would you suggest for busy practitioners to streamline these discussions?

Larkin: I'd first like to emphasize the importance of asking midlife patients about VMS. The menopause transition is a critical time to assess cardiovascular risk and focus on long-term health and wellness. Women experiencing VMS are at increased cardiovascular risk, so it's much more than a lifestyle issue.

Remember that the US Preventive Services Task Force is clear: Hormone therapy isn't indicated for primary prevention. However, that's different from addressing the symptomatic menopausal patient in front of you who may not be sleeping, is experiencing sexual dysfunction, and is generally miserable.



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I suggest a “red, yellow, green” approach to categorize patients:

Green patients

These are women who are symptomatic with moderate to severe VMS, are close to menopause [within 10 years of their final menstrual period], and have no significant cardiovascular risk factors, clotting history, or elevated breast cancer risk. For example, the 52-year-old sitting in front of you who is miserable but otherwise healthy [is] a great candidate for menopausal hormone therapy.

Red patients

These are women with clear contraindications to hormone therapy, such as a history of breast cancer, thromboembolic events, high cardiovascular risk, or prior cardiovascular events [such as] a stroke. For these patients, focus on nonhormonal options, such as fezolinetant or, if approved, elinzanetant, along with other off-label nonhormonal treatments.

Yellow patients

These are the intermediate cases. These women may have some risk factors that require a more nuanced discussion and consideration of patient preferences. If this isn't your area of expertise, consider referring these patients to a provider specializing in menopausal medicine.

Using this framework can help streamline your approach and build confidence in using FDA-approved nonhormonal options for patients who cannot or will not use hormone therapy. ■

Patient Care[®] ConsultantLive™

Promoting Early Identification and Timely Treatment of Obstructive Sleep Apnea

In this *Patient Care ConsultantLive* program, “Promoting Early Identification and Timely Treatment of Obstructive Sleep Apnea,” 2 internal medicine physicians with extensive experience in treating sleep disorders take a comprehensive look at the clinical landscape of obstructive sleep apnea (OSA), from its fundamental pathophysiology and profound negative impacts on health to diagnostic approaches and systemic barriers that challenge effective identification and treatment of this prevalent sleep disorder.

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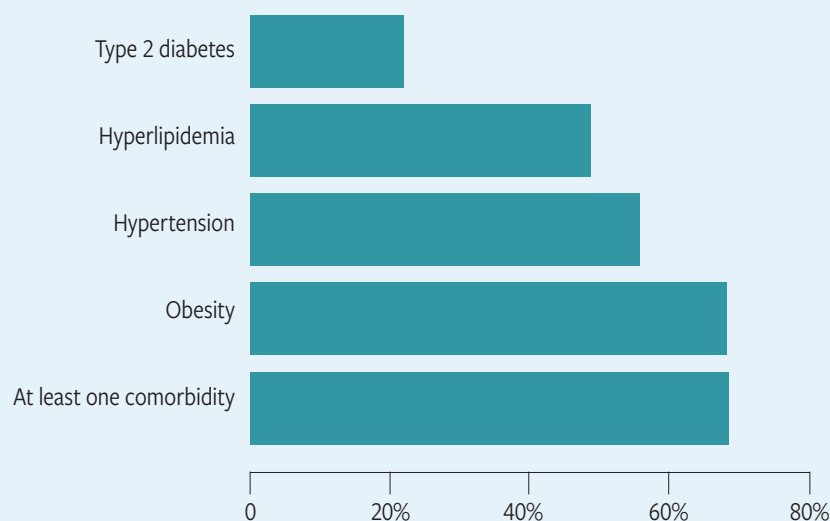
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By **Grace Halsey** *Senior Editor*

Obstructive Sleep Apnea

Aneesa Das, MD: To start today, I'd like to briefly explain how we define OSA for anyone who may not be completely familiar. Essentially, OSA occurs when we attempt to pull air into our lungs, creating negative pressure in the thorax, which can cause the airway to collapse. The vibration of the tissues leads to snoring, and the narrowing or collapse of the airway results in sleep apnea. Sleep apnea is defined based on 2 main events: obstructive apnea, [which is] when the airway closes completely, leading to a cessation of airflow for at least 10 seconds; and hypopnea, which involves a significant drop in airflow that results in a meaningful oxygen desaturation. Both events have similar negative effects

FIGURE 1. Common Comorbidities in OSA



Marshall NS, Wong KK, Liu PY, Cullen SR, Knuihan MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. *Sleep*. 2008;31(8):1079-1085. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2542953/>

on health outcomes. Hypopnea is just as concerning as apnea because breathing so minimally that oxygen saturation levels drop significantly is equivalent to not breathing at all.

We classify sleep apnea severity using the Apnea-Hypopnea Index (AHI), which is admittedly an imperfect scale, but it's the standard we currently have. The categories are:

Mild: AHI between 5 and 15

Moderate: AHI between 15 and 30

Severe: AHI over 30

Current guidelines indicate treatment for mild sleep apnea primarily to alleviate symptoms, but there are exceptions. For example, if a patient is undergoing major surgery, has cardiovascular comorbidities, or other risk factors, treatment might still be indicated. In contrast, moderate to severe OSA is typically treated universally due to the robust data linking these cases to adverse health outcomes.

OSA Burden and Impact on Health

Das: OSA is as common as asthma in the United States. When we define sleep apnea as an AHI of 5 or greater, an estimated 30 million Americans have OSA, yet only about 6 million have been diagnosed. This means we're just addressing the tip of [the] iceberg. The global prevalence is striking, with nearly 1 billion people worldwide likely to have sleep apnea. Addressing OSA—even in mild cases, depending on the context—can lead to substantial improvements in both symptoms and long-term health outcomes because there is a clear association between moderate to severe OSA and increased mortality. Over a 14-year span, individuals with moderate to severe OSA had a 33% mortality rate compared [with] 6% to 7% for those with mild or no sleep apnea. That's significant.

When we evaluate these patients, the classic presentation is often linked to metabolic syndrome,

[as] studies show a strong overlap. Patients with type 2 diabetes, hyperlipidemia, hypertension, and obesity are highly likely to also have OSA (**Figure 1**).

Jeanne Caligiuri, MD: In fact, more than 80% of people with metabolic syndrome also have OSA. Think about how many patients in a typical internal medicine practice have diabetes, hypertension, and hyperlipidemia. The majority of them likely have OSA, yet I'm not diagnosing 80% of those cases—and I'm sure I could do better.

Das: That's an important point. When we see a patient with these conditions, it should prompt screening for OSA. Recently, the American Heart Association emphasized the role of sleep in overall health, particularly untreated OSA, which is strongly associated with resistant hypertension. In fact, 83% of patients with resistant hypertension have sleep apnea. OSA is also linked to pulmonary hypertension and atrial fibrillation [AFib]. Untreated OSA increases the recurrence of AFib, even after ablation. Furthermore, untreated OSA has robust associations with stroke.

Caligiuri: A powerful example I share with patients about the impact of poor sleep on cardiovascular health is what happens during daylight saving time. In the spring, when we lose an hour, heart attacks increase by 24% the following day. Conversely, in the fall, gaining an hour results in a 21% decrease in heart attacks. Even very small disruptions in sleep can impact cardiovascular health.

Das: Daytime sleepiness is one of the most noticeable symptoms of interrupted sleep, though not everyone with severe OSA experiences it. Some patients don't even realize they're tired until they start treatment and feel the difference. I've had patients say, "I didn't realize how bad I felt until I started to feel better." Another critical public

health concern is drowsy driving. Studies show that drivers with OSA have a crash risk as much as 489% higher than those without it. Going back to daylight saving [time], crashes decrease by 24% in the fall when people gain an hour of sleep and increase by the same percentage in the spring when they lose an hour. OSA significantly contributes to this risk.

Risk Factors for OSA

Caligiuri: I do discuss sleep with my patients, but they rarely come in specifically to be evaluated for OSA. Instead, they present with fatigue or other symptoms. Honestly, I can't think of a single woman [younger than] 55 [years] who doesn't mention being tired—and it often picks up again in older patients. Regarding cardiovascular and other systemic effects of OSA, I'd estimate that at least 75% of my patients are affected. Screening and addressing these issues need to be a bigger priority in primary care.

Das: Given that underdiagnosis is such an issue, Jeanne, how confident do you feel in your ability to identify patients at risk for OSA? What signs and symptoms are you looking for when you assess for OSA (Figure 2)?

Caligiuri: I've been practicing for 20 years. Ten years ago, I wouldn't have been confident at all, but now I'd say I'm very confident. As for screening, I think about 2 types of office visits: wellness visits and follow-ups. During follow-up visits, when patients are checking in about diabetes, hypertension, reflux, or even depression, I listen for fatigue, nocturia, uncontrolled high blood pressure, weight gain, or the onset of hypothyroidism. [However], the biggest trigger for me is when patients say they're tired or sleepy.

Das: Studies show that the average time between symptom onset and OSA diagnosis is 7 years—that's

FIGURE 2. Risk Factors for OSA

- Excess weight
- Male sex
- Post menopause
- Older age
- Hypertension
- Loud snoring
- Diabetes
- Family history of sleep apnea
- Narrowed airway
- Small mandible
- Smoking

Obstructed sleep apnea. Mayo Clinic. Updated July 14, 2023. Accessed January 9, 2025. <https://www.mayoclinic.org/diseases-conditions/obstructive-sleep-apnea/symptoms-causes/syc-20352090>

a huge delay. [Although] the gap is even larger among [minority populations], it's still significant across all populations. The responsibility falls on all of us to recognize these signs earlier.

Thinking about risk factors, male gender is a risk factor, but only until women hit menopause when their risk of OSA increases—even without weight changes. In fact, there's a 20% increase in OSA prevalence at the same BMI [body mass index] post menopause. Aging also plays a role, as tissue laxity and other comorbidities contribute. Older, thinner patients might have a higher risk than we would've previously thought.

Caligiuri: When it comes to discussing OSA risk factors, the top barrier tends to be lack of time during consultations, and that is No. 1 for me. It's a little easier to focus on sleep-related issues during follow-up visits when patients bring up specific complaints, but during prevention and wellness visits, I feel the time crunch even more.

I get 40 minutes for a wellness visit, and I make it a point to ask everyone 5 critical questions every year. I explain that the first 2 questions are the most important and might take up the majority of the visit. If we don't get to everything, I let them know we'll need to schedule another visit to cover the rest.

The first question—by far the greatest predictor of how long someone will live and their overall health and happiness—is about the

quality of their relationships. The second question, which is almost as important, is about sleep quality and quantity. Questions 3, 4, and 5 cover diet, exercise, and water intake. These all connect, but sleep and meaningful relationships are foundational. If you're not sleeping well, it's hard to be emotionally available to connect with others. Similarly, you need good sleep to exercise effectively, eat well, and maintain healthy relationships. Everything ties back to these first 2 questions.

Loneliness is a killer; that's why I spend a significant amount of time addressing depression, isolation, and marital discord during visits. Sleep is the second most critical factor, and I often feel the pressure of time when trying to dive into why a patient isn't getting restorative sleep. Are they snoring? [Are they] having apnea spells? [Are they] waking up with anxiety? This is such a big issue. Sometimes I tell my patients, "We've spent most of this visit talking about sleep, and we're not going to fix it all in 1 night or 1 appointment. Let's schedule another visit to address the rest of this wellness check." That's how seriously I take it.

Das: If you don't ask, you just won't know; that's part of the challenge. Often, patients come in with their own agenda of issues they want to address, which may not include sleep concerns. Risk factors will be obvious to us with some patients, so we'll get to the

questions, but we want to make sure we're not missing others who might not fit the typical profile. Asking something as simple as "Do you feel rested?" can help catch those cases. Going beyond that, the key is thinking early and screening proactively.

Screening and Treatment for OSA

Das: Let's talk about screening and the available tools. Remember, all screening assessments are just that—screening tools, not diagnostic tests. They're designed to expedite the time from symptom onset to diagnosis. Recognize their limitations. For example, the STOP-Bang questionnaire was developed for preoperative patients to assess sleep apnea risk, but I like it because it's quick [and] easy, and much of it can be assessed by nursing staff before you even see the patient. STOP-Bang stands for:

- S:** Do you snore?
- T:** Are you frequently tired?
- O:** Have you observed apnea or choking episodes?
- P:** Do you have high blood pressure, or are you being treated for it?
- B:** Is your BMI over 35?
- A:** Are you [older than] 50 years?
- N:** Is your neck circumference greater than or equal to 40 cm?
- G:** Are you male?

If a patient scores [a] 3 [or] 4 out of 8, they're considered intermediate risk. A score of 5 [to] 8 indicates high risk. Low risk, of course, doesn't mean no risk. For insurance purposes, symptoms [such as] daytime fatigue or observed apnea are often covered,

whereas snoring alone typically isn't. This tool is simple, time efficient, and a great way to capture at-risk patients.

Das: At [The Ohio State University], most providers probably refer to specialists, but that's not the case nationwide. Interestingly, 75% of the audience today—mostly primary care clinicians—say they feel very comfortable treating it. This underscores why we're discussing this topic—it's great to see primary care so involved!

When treating obstructive sleep apnea, I break it into 4 main approaches:

Positive airway pressure (PAP) therapy:

[This is] the gold standard. It works for most patients when used consistently.

Oral appliances: [This is] a good first-line option for mild to moderate sleep apnea.

Weight loss and behavioral modification:

[This] includes positional therapy [avoiding sleeping on your back], reducing alcohol intake at night, and avoiding respiratory suppressants.

Surgical or neuromodulation therapy:

[This is] reserved for patients who can't tolerate other treatments or have significant anatomical issues. Neuromodulation, for instance, involves an implant that senses breathing and stimulates the tongue to increase airway space.

For PAP therapy, early adherence is critical. Data show that patients who use their device consistently in the first 3 days to 1 week are much more likely to remain adherent long term. Key factors include:

Symptom severity: Patients with more severe symptoms are naturally more motivated.

Realistic expectations: It's not always easy at first, and adjustment takes time.

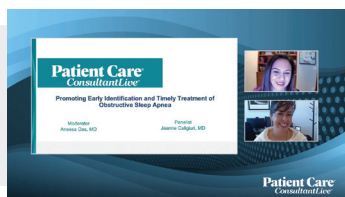
Support systems: Partners who encourage adherence significantly improve outcomes.

Troubleshooting resources: Ensuring patients have access to help for mask leaks or discomfort can make a big difference.

I should mention here that PAP therapy has become easier with innovations [such as] autotitrating [continuous] PAP [CPAP] devices, which adjust pressure based on patient needs. There are also more mask options now, from lightweight nasal pillows to full-face masks. Patients can even track their own adherence with apps that provide instant feedback, which has improved [adherence] significantly. Remote monitoring has truly been a game changer.

For patients who don't tolerate CPAP, oral appliances can be a good alternative. [Although] they're less effective for severe cases, around 25% of patients [with severe symptoms] still respond to them. They work best in younger, thinner patients with mild to moderate sleep apnea or positional apnea.

Lastly, weight management is essential. Obesity contributes to sleep apnea, so addressing it through diet, exercise, bariatric surgery, or medications like [glucagon-like peptide-1] agonists can improve outcomes. In fact, a recent [The] *New England Journal of Medicine* study showed that tirzepatide reduced both BMI and AHI, leading to [the] FDA fast tracking it for [OSA] treatment. ■



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