Experts Still Confounded by How to Prevent, Manage Hypoglycemia

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Hypoglycemia has been targeted as an immense public-health problem, and yet clinicians, regulators, and health officials continue to struggle to figure out how to prevent the condition and better target and manage those at highest risk.

That was the takeaway from a daylong meeting held by the US Food and Drug Administration on September 12. The agency brought together federal officials, patient advocates, geriatricians, and endocrinologists to discuss the prevention of adverse drug events associated with hypoglycemia in older patients.

Hypoglycemia can occur with many medications, and in both those with and without diabetes. It is most common — and most dangerous — in those with diabetes taking insulin and/or sulfonylureas, said speakers at the meeting.

That in and of itself is frustrating, said Robert Lash, MD, a professor at the University of Michigan School of Medicine, Ann Arbor, who spoke on behalf of the Endocrine Society.

“It’s amazing that we are still addressing questions of hypoglycemia after so many years of using these two classes of medications,” said Dr Lash.

ER Visits for Hypoglycemia Are "Tip of the Iceberg"

Robert E Ratner, MD, chief medical and scientific officer at the American Diabetes Association, said data show that patients taking a combination of insulin and sulfonylureas were 2.5 times more likely to experience hypoglycemia.

Insulin is the second-most common drug associated with emergency-room visits for adverse events, said Christine Lee, PharmD, an FDA staffer with the agency’s Safe Use Initiative, which is bringing together public and private entities to address medication errors and management.

Nadine Shehab, PharmD, MPH, with the Centers for Disease Control and Prevention (CDC) medication safety program, concurred. She said that of 1.3 million annual emergency-room visits for adverse drug events, 13% involve diabetes medications. Two-thirds of the visits are for severe hypoglycemia, with shock, loss of consciousness or seizures, a fall or injury, or altered mental status, said Dr Shehab, adding that a third resulted in hospitalization.

“We need to recognize hypoglycemia as an outcome, not as a side effect,” said Dr Ratner, adding that the ER visits and hospitalizations are just the tip of the iceberg. Dr Ratner cited data showing that almost 80% of those with type 1 diabetes and more than half of those with type 2 experience hypoglycemia at least once a month. Many have it weekly, he said.

Hypoglycemia is often unrecognized by patients or clinicians but carries significant morbidity, he said, noting, for instance, that even asymptomatic hypoglycemia can cause cardiac side effects such as QT prolongation and flattening of the T wave on ECG.

Missed Meals, Food Insufficiency

Older patients with diabetes tend to be particularly vulnerable to hypoglycemia, said attendees. Hypoglycemia unawareness is an issue, particularly in those who might be cognitively impaired. But missed meals — or not having enough food or access to food — is also a huge problem.

Individuals aged 80 or over are 2.5 times more likely to have an ER visit for an insulin adverse event and five times more likely to be hospitalized, said Dr Shehab.

The CDC has been able to determine a causative factor for about a fifth of the insulin-related hypoglycemia emergencies and found that almost half were related to meals, she said.

Food insufficiency — not having enough food or enough money to buy food — is a problem that affects many Americans, no matter their income level, said Mary Julius, RDN, CDE, with the Department of Veterans Affairs (VA).

She urged clinicians to ask every patient about food insufficiency, noting that, in addition to being good practice and compassionate care, it is also reimbursable (through the ICD 10 code 59.4).
"The number-one cause of a hypoglycemic event is a missed meal or a food-insufficient meal," said Ms Julius.

The VA will soon ask all patients in its facilities — not just those with diabetes — about food insufficiency. The screening question — which asks, "are there times in the past 3 months when the food for you just did not last and there was no money to buy more?" — will be incorporated into the medical record.

The CDC data also show that another major factor contributing to insulin-related adverse events was patients taking the wrong insulin or confusing the dose or units to be used.

**Glycemic Control Too Tight**

Experts at the meeting also found fault in what they see as the tendency to overzealously treat diabetes — pushing older diabetic patients to reduce HbA$_{1c}$ to levels that are not merited, given the individual's overall health or predicted lifespan.

Len Pogach, MD, MPH, national program director for diabetes for the VA, asked rhetorically, "Do we have problems understanding that overtreatment may be a problem?"

In his view, the answer is a definitive yes. Some clinicians feel they must reduce HbA$_{1c}$ below 7% in older patients to meet performance measures. "There is a lot of misinformation out there," he said.

Medha Munshi, MD, director, Joslin Geriatric Diabetes Program, Beth Israel Deaconess Medical Center, Boston, Massachusetts, said that it's possible to deintensify an older patient's insulin regimen without compromising glycemic control, as she described in a 2016 research letter (JAMA Intern Med. 2016;176:1023-1025).

"The problem is, we do not have good evidence on how to deintensify regimens," said Dr Munshi.

She added that researchers need a better outcome measure for older patients to determine how to avoid hypoglycemia: "A$_{1c}$ alone is not adequate."

**Homing In on Those at Risk**

Not every older patient with diabetes will be at risk for hypoglycemia, but, to date, it has not been clear how to target those who might be most vulnerable.

Kaiser Permanente of Northern California has developed and validated a way to gauge that risk, using its electronic medical record system to identify potential risk factors in a population of type 2 diabetic patients.

Results of an internal and external validation of that risk tool were published online in August, as reported by Medscape Medical News and discussed at the meeting by Kaiser research scientist Andrew Karter, PhD.

The organization found that in its internal validation sample, 2% of older people with diabetes were at high risk for hypoglycemia, almost 11% were intermediate risk, and the remainder were low risk.

Kaiser is "trying to figure out how we are going to use this tool," said Dr Karter. One outcome might be to create an automated alert in the electronic medical record for patients who could potentially fall into the high- or immediate-risk buckets. Another possibility is to have a "triage" team attempt to identify the cause of a previous hypoglycemic event and then send the patient for behavioral counseling or to a nutritionist or a social worker, he said.

The Mayo Clinic has also been using the Kaiser risk-prediction tool among some 53,000 type 2 diabetic patients in 90 primary-care practices that are part of its Transforming Clinical Practice Initiative. Mayo found that 1.35% were categorized as high risk and 12.2% at intermediate risk, said Nilay Shah, PhD, associate professor of health services research, Mayo Clinic, Rochester, Minnesota.

The biggest risk factor was one or two previous ER visits for insulin-related hypoglycemia, he said. No differences have been observed for gender or language spoken, but unmarried patients were at much higher risk, as were African Americans. Mayo also observed a large variation in risk at each practice, said Dr Shah.

Mayo is now looking at instituting a more intensive medication-therapy management program whereby pharmacists would contact patients deemed to be at high risk. The organization is also piloting the addition of clinical-decision support tools that give clinicians real-time data, said Dr Shah.

**Moving Forward**
While many different efforts are under way in the United States to try to address hypoglycemia, none seem to have yet borne fruit.

The National Action Plan for Adverse Drug Event (ADE) Prevention was launched in 2014 and continues to have diabetes drugs as a focus, said officials.

The VA is beginning its Implementation Plan for Preventing Hypoglycemia. Some 1.6 million veterans have diabetes, 70% of whom are 65 and older, said Dr Pogach, adding that 30% receive insulin and 60% have serious comorbid conditions. The plan will focus on shared decision-making with patients, attempting to tailor what makes the most sense for that individual, he said.

And the Endocrine Society is pushing ahead with its Hypoglycemia Quality Collaborative, fostered by 18 organizations, including clinicians, diabetes educators, health systems, pharmaceutical companies, academic medical centers, and patient advocates.

Dr Lash said he agreed with Dr Ratner that it was imperative to have an outcome measure specific to hypoglycemia. The Centers for Medicare and Medicaid Services has announced funding opportunities to develop such a measure. The Endocrine Society is working on submitting an application for a measure that would look at hypoglycemia in the type 2 population, said Dr Lash.

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