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# Managing Hypoglycemia in Primary Care

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**Dr. Tenzer-Iglesias** discloses that she is on the advisory board for Forest Pharmaceuticals.

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**LEARNING OBJECTIVES:**

- Compare the risk of hypoglycemia among glucose-lowering agents.
- Identify patient risk factors and behaviors that increase the risk of hypoglycemia.
- Describe techniques physicians may use to identify patients at risk for hypoglycemia.
- Describe patient education strategies regarding hypoglycemia.

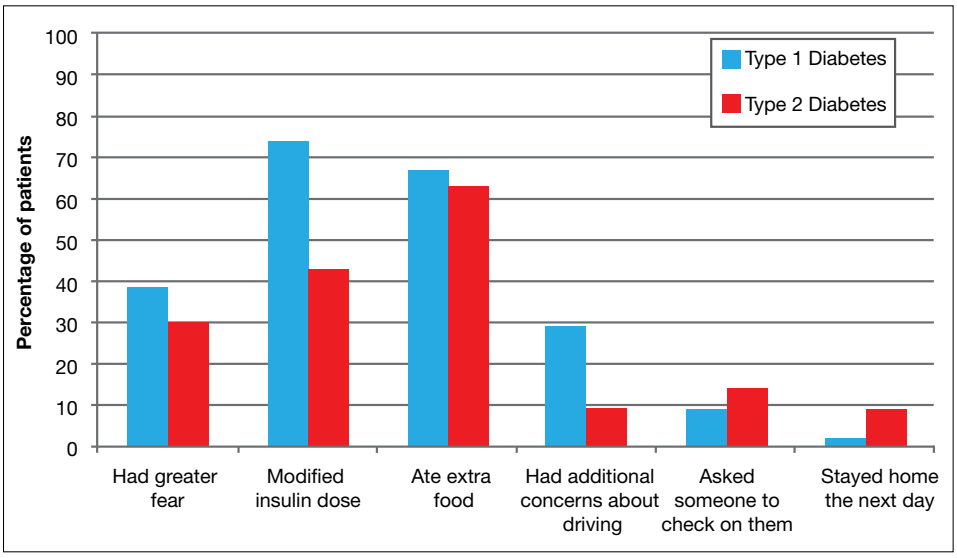
## Overview

Hypoglycemia is one of the most serious complications associated with glucose-lowering therapy and is a barrier to initiating, intensifying, and optimizing therapy, as well as long-term adherence.[1-4] One survey found that, following a mild-to-moderate hypoglycemic episode, 74% of patients with type 1 diabetes mellitus (T1DM) (n = 202) and 43% with type 2 DM (T2DM) (n = 133) modified their insulin dose (**FIGURE**).[1] Following a severe hypoglycemic episode, 78% and 58% of T1DM and T2DM patients, respectively, modified their insulin dose.[1] The survey also found that two-thirds of patients consumed extra food to avoid a subsequent hypoglycemic episode. The consequences of hypoglycemia are numerous and include diminished patient psychological well-being and quality of life, fear and anxiety, and reduced productivity—the impact being greater following a severe hypoglycemic episode.[1,2,5-9] For example, 29.9% of patients with T2DM were more fearful that a future hypoglycemic episode would occur following a mild or moderate hypoglycemic episode compared with 84.2% of patients following a severe hypoglycemic episode.[1]

Reports collected from a series of focus groups provide greater insight into the impact of hypoglycemia on the daily lives of patients with T1DM or T2DM (N = 18).[8] The 5 themes that emerged from the results of this study are detailed in **TABLE 1**.

Hypoglycemia is associated with important DM-related outcomes, such as poor glycemic control, likely resulting from modification and adjustment to the treatment plan.[3,4] Severe symptomatic

**FIGURE Impact of mild-to-moderate hypoglycemia on patients[1]**




hypoglycemia was also found to be associated with an increased risk of death in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trials.[10,11] In the ADVANCE study, the risk of all-cause mortality was significantly higher in individuals who experienced a severe hypoglycemic episode (blood glucose < 50 mg/dL and requiring assistance) compared with those who did not (19.5% vs 9.0%, respectively; hazard ratio [HR], 3.27; 95% confidence interval [CI], 2.29-4.65). In addition, the ADVANCE trial reported that a major macrovascular event (eg, cardiovascular death, nonfatal myocardial infarction, non-fatal stroke) was observed in 16.8% of patients who reported severe hypoglycemia compared with 10.2% of those who did not. The respective rates for a major microvascular event (eg, new or worsening nephropathy, retinopathy) were 11.5% in patients who had experienced a severe hypoglycemic event and 10.1% in those who had not.

Other investigations have demonstrated an increased risk of dementia in patients who experienced severe hypoglycemia.[12,13] Data from the Kaiser Permanente of Northern California registry showed that, compared with patients without hypoglycemia, patients with T2DM who had experienced single or multiple episodes of hypoglycemia requiring hospitalization or emergency department care had a graduated increase in risk for cognitive impairment: 1 episode (HR, 1.26; 95% CI, 1.10-1.49), 2 episodes (HR, 1.80; 95% CI, 1.37-2.36), and 3 or more episodes (HR, 1.94; 95% CI, 1.42-2.64).[12]

Finally, the cost of health care is higher in patients who experience hypoglycemia.[9] Moreover, the mean annual cost of hypoglycemia-associated claims for patients treated with human insulin (vial and syringe) was approximately $1500 compared with $620 for those treated with insulin analogs.

## Definition of hypoglycemia

Although there is no consensus on the definition of hypoglycemia in DM, the American Diabetes Association (ADA) currently defines hypoglycemia as a blood glucose level <70 mg/dL.[14] The ADA further categorizes hypoglycemia as mild-to-moderate (40-69 mg/dL) or severe (<40 mg/dL). The 2012 ADA standards, however, provide no additional criteria (eg, the ability to self-manage hypoglycemia, hypoglycemic episodes requiring third-party assistance), which are frequently used in clinical trials to differentiate mild or moderate from severe hypoglycemia. A 2005 ADA Workgroup on Hypoglycemia defined severe hypoglycemia as "an event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions."[15] The working group also noted that documented hypoglycemia is "an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70 mg/dL."

## Risk factors

Hypoglycemia results from an excess of insulin action relative to blood glucose. In addition to glucose-lowering medications (discussed below), there are many risk factors for hypoglycemia. These include a longer duration of DM, decreased glucose intake or absorption (eg, a missed or delayed meal, gastroenteritis, vomiting); decreased glucose production (eg, from alcohol consumption, liver disease); increased glucose utilization (eg, physical exercise); and slowed renal clearance of insulin and most glucose-lowering drugs.[16,17] Additional risk factors for hypoglycemia identified in the ACCORD trial include female gender, African-American

**TABLE 1** **Themes describing the impact of diabetes on patients' lives[8]**

| Theme | Focus group comments |
|---|---|
| Friends, family, neighbors need hypoglycemia education. | One woman reported that she awoke to her husband and daughter pouring orange juice into her mouth. Her husband had noticed that she was sweating profusely while taking a nap. He checked her blood glucose and found it was 24 mg/dL. |
| Leaving home (to run an errand or travel out of town) is a concern. | Several participants reported measuring their blood glucose before leaving home for long or short durations (especially before driving), or eating a snack prior to departure. |
| Overeating occurs when treating hypoglycemia. | "If I'm really low [blood sugar]…, I'll eat until I feel better. You got the bad things that happen to you when you run high all the time, but the bad things that happen to you when you run low happen right now." |
| Maintaining a daily routine is important to managing diabetes and avoiding hypoglycemia. | Most worked hard to maintain a regular work, eating, and exercise schedule, while feeling more likely to experience a hypoglycemic episode if their schedule varied. |
| Hypoglycemia is a limitation that affects glycemic control, one's physical abilities, and overall quality of life. | Hypoglycemia was believed to limit physical activity and blood glucose management, as well as being a barrier to successful weight management and an impediment to a high quality of life. |

**Source:** Sutton L, Chapman-Novakofski K. Qual Health Res 21(9):1220-1228, copyright © 2011 by Sage Publications. Reprinted by Permission of SAGE Publications.

race (compared with non-Hispanic whites), and less than a high school education (compared with college education). In addition, the risk of hypoglycemia requiring medical assistance was found to increase at a rate of 3% for each 1-year increase in age at baseline.[18]

Increased glucose utilization during exercise can lead to hypoglycemia during, and for many hours following, a workout. In one study of adolescents with T1DM, an increase in glucose utilization was observed during and for 90 minutes after exercise, and then again from 7 to 11 hours after exercise.[19] This biphasic curve of hypoglycemia indicates there is an early, as well as a delayed, risk for nocturnal hypoglycemia following afternoon exercise. Another study showed a similar pattern commonly observed with nocturnal hypoglycemia.[20] The number of nocturnal hypoglycemic episodes was related to exercise intensity, with intermittent high-intensity exercise more likely to induce nocturnal hypoglycemia than intermittent moderate-intensity exercise. Thus, while physical activity is a cornerstone of DM management, patients should be advised to maintain a regular exercise pattern and remain vigilant regarding the signs and symptoms of hypoglycemia–including delayed hypoglycemia–and use nutrition supplementation as needed.

While a relative excess of insulin in healthy individuals causes up-regulation of counter-regulatory mechanisms to maintain glucose homeostasis, these mechanisms are often impaired in patients with DM. Specifically, early in T1DM and later in T2DM, the circulating insulin level does not fall, and the glucagon level does not rise in response to a decrease in blood glucose level. In addition, there is an attenuated sympathetic response, primarily involving epinephrine, which is largely responsible for the development or worsening of impaired hypoglycemia awareness. Individuals with hypoglycemia unawareness have a 6- to 17-fold increased risk of severe hypoglycemia compared with individuals who have normal hypoglycemia awareness.[21-23]

## Intensive therapy

While the microvascular benefits of improved glycemic control are well established, the results of the ACCORD, ADVANCE, and Veterans Affairs Diabetes Trial demonstrate that focusing treatment on attaining a lower glycated hemoglobin (A1C) level may not be optimal for all patients.[24-30] The most recent guidelines issued by the American Association of Clinical Endocrinologists/American College of Endocrinology, and the American Diabetes Association recommend individualizing the A1C goal in order to achieve the optimal benefit in terms of efficacy and risk.[14,31,32] Patients in whom less stringent A1C goals (ie, 7.5%-8.0%) are appropriate include patients with a history of severe hypoglycemia, limited life expectancy, advanced micro- or macrovascular complications, extensive comorbidities, and those with long-standing DM in whom

the A1C target is difficult to attain despite aggressive intervention.[32,33]

## Selection of glucose-lowering therapy

Glucose-lowering agents are a common cause of hypoglycemia, with some agents more likely to produce hypoglycemia than others (**TABLE 2**).[14,31,32] For example, in the A Diabetes Outcome Progression Trial (ADOPT), a self-reported hypoglycemic event was reported by 38.7% of patients treated with glyburide, 11.6% of patients treated with metformin, and 9.8% of patients treated with rosiglitazone (glyburide vs rosiglitazone; $P \leq .01$).[34] Consistent with their mechanisms of action, these glucose-lowering agents can be broadly categorized as having either a low- or high-risk of hypoglycemia.[31] The meglitinides, insulin, and sulfonylurea classes—all of which increase the insulin level in a glucose-independent manner—comprise the high-risk category.

The remaining classes of glucose-lowering agents—alpha-glucosidase inhibitors, ergoline derivatives (eg, bromocriptine), bile acid sequestrants (eg, colesevelam), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor (GLP-1R) agonists, biguanides (eg, metformin), amylin analog (eg, pramlintide), and thiazolidinediones (TZDs)—are considered low-risk for hypoglycemia as they lower blood glucose by 1 or more mechanisms other than increasing the blood level of insulin, or work in a glucose-dependent manner. For example, metformin decreases hepatic glucose production and is a mild insulin sensitizer, while the TZDs are strictly insulin sensitizers. The GLP-1R agonists and DPP-4 inhibitors increase insulin secretion, but do so in a glucose-dependent manner. As a consequence, the low-risk categories of these agents are generally associated with a minimal risk of hypoglycemia when used as monotherapy. Severe hypoglycemia is an infrequent occurrence with these agents.[31,34-40] However, the risk of hypoglycemia increases when a low-risk medication, specifically a DPP-4 inhibitor, GLP-1R agonist, or TZD, is used concomitantly with insulin or an insulin secretagogue. In this situation, it is recommended that the dose of either agent be reduced, in addition to advising the patient to monitor glucose levels for hypoglycemia during the transition period to the new regimen.

Within the high-risk category, the meglitinides are the least likely to cause hypoglycemia, while insulins are the most likely.[31] Among insulins, the slower onset, delayed peak, and longer duration of action of regular human insulin results in an increased risk of hypoglycemia compared with the rapid-acting insulin analogs aspart, glulisine, and lispro. Rapid-acting insulin analogs can cause a more immediate hypoglycemia, particularly if food intake is inadequate or delayed. Similarly, the time-action profile of neutral protamine Hagedorn (NPH) insulin, coupled with highly variable intrapatient absorption, results in a higher risk of hypoglycemia compared with the relatively flat time-action profile and more consistent absorption of the long-acting insulin analogs detemir and glargine.[31] Among the sulfonylureas, hypoglycemia is more common with glyburide than glimepiride and glipizide.[31]

Concern about hypoglycemia has been a factor in the development of new glucose-lowering medications. Two investigational medications represent new treatment options for lowering blood glucose with a low incidence of hypoglycemia. Insulin degludec, which is under review by the US Food and Drug Administration (FDA), is an ultra-long-acting insulin with an elimination half-life longer than 24 hours, thereby resulting in a relatively flat and consistent blood glucose-lowering effect for more than 42 hours.[41,42] In patients with T1DM and a baseline A1C of 7.5% to 8.5% (N = 332), rates of overall and severe hypoglycemia with insulin degludec were similar to insulin glargine in phase 3a trials over 26 or 52 weeks, while rates of nocturnal hypoglycemia were lower with insulin degludec (rate ratio [RR], 0.68; 95% CI, 0.50-0.93).[43] Similar rates of overall confirmed hypoglycemia were observed in an open-label trial of patients with T1DM and a baseline A1C ≤10% (N = 629),

**Within the high-risk category of glucose-lowering agents, the meglitinides are the least likely to cause hypoglycemia, while insulins are the most likely.**

while nocturnal hypoglycemia was less frequent with insulin degludec compared with insulin glargine (RR, 0.75; 95% CI, 0.59-0.96).[44] In patients with T2DM treated for 1 year, the rates of confirmed hypoglycemia (11.09 vs 13.63 episodes/patient-year; $P = .0359$) and nocturnal confirmed hypoglycemia (1.39 vs 1.84 episodes/patient-year; $P = .0399$) were significantly lower in patients treated with insulin degludec compared with insulin glargine, respectively, both in combination with prandial insulin aspart ± metformin ± pioglitazone.[45]

Another class of investigational agents is the sodium-glucose cotransporter-2 (SGLT-2) inhibitors, which lower blood glucose by inducing a mild osmotic diuresis and increasing the urinary excretion of glucose. Two of these agents, dapagliflozin and canagliflozin, are

**TABLE 2** **Relative risk of hypoglycemia among available glucose-lowering agents**[14,31,32]

| Glucose-lowering agent | Relative risk of hypoglycemia |
|---|---|
| Alpha-glucosidase inhibitor | + |
| Bromocriptine | + |
| Colesevelam | + |
| DPP-4 inhibitor | + |
| GLP-1R agonist | + |
| Insulin | ++++ |
| Meglitinide | ++ |
| Metformin | + |
| Pramlintide | + |
| Sulfonylurea | +++ |
| Thiazolidinedione | + |

DPP-4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor.

+, no hypoglycemia; ++, infrequent hypoglycemia; +++, occasional hypoglycemia; ++++, frequent hypoglycemia

currently under review by the FDA. Over 48 weeks, the addition of dapagliflozin 5 mg or 10 mg to pioglitazone 30 mg or 45 mg resulted in a hypoglycemic episode in 2.1% and 0% of patients, respectively, compared with 0% in patients treated with the addition of placebo.[46] There were no episodes of hypoglycemia requiring external assistance. In a 12-week study, the addition to metformin of canagliflozin in daily doses ranging from 50 to 600 mg was associated with reductions in the A1C level of 0.70% to 0.95% compared with 0.74% for sitagliptin 100 mg/d and 0.22% for placebo.[47] Symptomatic hypoglycemia occurred in 0% to 6% of the canagliflozin patients compared with 5% and 2% of sitagliptin and placebo patients, respectively.

## Patient self-management

Diabetes is a disease in which outcomes are largely determined by patient self-management, thus a collaborative relationship between family physician and patient is of the utmost importance.[48] This point was recently identified by a survey of patients with T2DM (n = 1609), general practitioners (n = 818), and DM specialists (n = 697).[49] Rather than more time allocated to office visits, patients preferred easier access to their physician. Furthermore, patients wanted more information and greater involvement in their own care, perhaps because patients demonstrated the understanding that DM is a serious health issue. The results of this survey underscore the importance of ensuring that each patient has the knowledge and skills required to self-manage their DM, and that patient's concerns, beliefs, and values are addressed in treatment decisions.

Hypoglycemia is a concern for most patients with DM that should be discussed at the time of diagnosis and routinely thereafter. Patients should be assured that an important goal of therapy is minimizing the risk of adverse events, including hypoglycemia, and that treatment will be modified as needed. Patients should also be reminded of the importance of self-management and the benefits of working with their physician to set goals and optimize treatment.

Following the initiation of treatment, patients should be routinely asked about hypoglycemic episodes, how they were recognized, and what was done to manage such events. The patient should also be asked about the impact a hypoglycemic episode has had on subsequent treatment, and whether concerns persist regarding the treatment plan. Inquiring about daily work, school, and home life can also provide valuable insight into the patient's support system.

## Patient education

Beginning at the time of diagnosis, patient and caregiver education is a cornerstone of DM management. In addition to a consideration of cultural beliefs and patient background, DM education should be provided at a level appropriate for the patient's health literacy and numeracy, as both have been shown to have a significant impact on glycemic control and microvascular complications.[50-52] Limited health literacy (ie, the ability to obtain, process, and understand basic health information and services needed to make appropriate health decisions and follow instructions for treatment), or restricted numeracy (ie, the degree to which individuals have the capacity to access, process, interpret, communicate, and act on numerical, quantitative, graphical, biostatistical, and probabilistic health information needed to make effective health decisions) contribute to poor DM-related outcomes through limited disease knowledge and symptom recognition, greater difficulty interpreting food labels and estimating portion sizes, as well as lower self-efficacy.[51,53-59] Factors shown to be associated with lower numeracy include older age, non-white race, fewer years of education, lower reported income, and lower literacy.[51] In fact, numeracy may have a greater impact on glycemic control than literacy.[51,52]

## Hypoglycemia education

Strategies to manage hypoglycemia can be categorized into 3 groups: (1) prevention, or at the very least, risk reduction; (2) treatment of a hypoglycemic episode; and (3) modification of the DM treatment plan following a hypoglycemic episode. Each of these factors is depen-

dent on patient knowledge and action, which can be facilitated by the collaborative development of a written action plan by the physician, or other health care team member, and the patient.

To prevent or reduce the risk of hypoglycemia, it is important that the patient understands and agrees to adhere to all aspects of the treatment plan in terms of both medication and lifestyle. The signs and symptoms of hypoglycemia should be reviewed and the patient advised that not all symptoms may occur during an episode.[16] As noted earlier, detection of these symptoms by the patient is often difficult since hypoglycemic episodes often occur during sleep, and many patients with DM have diminished or absent hypoglycemia awareness.[22,60,61] While the patient's awareness of hypoglycemia is often caused by the perception of 1 or more neurogenic symptoms, educating the patient's family, particularly regarding neuroglycopenic symptoms, is recommended as these individuals may be helpful in identifying the early signs and symptoms of hypoglycemia (**TABLE 3**).[16]

Another important step in the prevention of hypoglycemia is cautioning the patient against taking any prescription, nonprescription, or herbal medication without first checking with a member of the DM care team. Additionally, a plan for self-monitoring blood glucose (SMBG) should be developed by the physician, or other health care team member, and the patient. The patient should also be trained to test and interpret the results. It is of paramount importance that the patient understands the appropriate actions to take based on SMBG results, whether it is a routine adjustment in medication dose or more immediate steps required in response to a hypoglycemic episode. A written action plan is instrumental in this regard, particularly if the patient requires assistance. The plan should describe the specific treatment to implement, including when to call 911 based on signs, symptoms, and blood glucose level. Since the action plan may not be readily available at the time of a hypoglycemic episode, it is recommended that the patient and family become familiar with, and periodically review, the plan.

**To prevent or reduce the risk of hypoglycemia, it is important that the patient understands and agrees to adhere to all aspects of the treatment plan in terms of both medication and lifestyle.**

**TABLE 3 Signs and symptoms of hypoglycemia[16]**

| Neuroglycopenic | Neurogenic |
|---|---|
| Cognitive impairment | Palpitations |
| Behavioral changes | Tremor |
| Psychomotor abnormalities | Anxiety/Arousal |
| Seizure | Sweating |
| Coma | Pallor |
| | Hunger |
| | Paresthesia |

Once the acute hypoglycemic episode has resolved, it is imperative that the cause(s) be identified. The patient should clearly understand how and when to involve the primary care provider in this process. For example, if the cause is readily apparent to the patient, such as missing a meal, vigorous exercise, or excessive alcohol intake, communication with the primary care provider might be delayed until the next office visit. Patients should be asked if they have made any changes to the treatment plan (eg, reducing medication doses, eating snacks). In addition, fear or anxiety relating to hypoglycemia should be investigated and addressed as appropriate. If the cause of the hypoglycemia is not readily apparent to the patient, and if moderate or severe symptoms were experienced, the action plan should include instructing the patient to contact the primary care provider immediately following resolution of the hypoglycemic episode.

Depending on the cause of hypoglycemia, changes to the treatment plan may include adjusting medications, timing or dosages, revising the A1C target level, modifying food intake including snacks (ie, content, timing, quantity, and type of food), and discussing the appropriate steps to take before and after exercise. This is also an opportune time to review the cues for hypoglycemia with the patient.[62] For patients with hypoglycemia unawareness, complete avoidance of hypoglycemia for 2 to 3 weeks is often effective in restoring the attenuated sympathetic response to abnormal glucose counterregulation.[16] A rise in epinephrine concentration and a return of adrenergic symptoms during hypoglycemia are thought to be primarily responsible for the improvement in hypoglycemic awareness.[63] An educational intervention aimed at improving hypoglycemia awareness is also suggested.

## Educational intervention

Many avenues to educating patients about hypoglycemia awareness have been investigated. One approach focuses on interrupting the cycle of frequent hypoglycemia that often leads to an increased risk of future

hypoglycemia.[64] The intervention consisted of lessons, lasting 90 minutes each, offered over the course of 5 weeks. Patients were trained in symptom awareness by using diaries and performing blood glucose estimates. After 6 months, several improvements were observed in the intervention group compared with the control group, including increased hypoglycemia awareness ($P$ = .024), a higher threshold for detection of low blood glucose ($P$ = .02), and better treatment of low blood glucose ($P$ = .03). In addition, the number of undetected hypoglycemic episodes ($P$ = .01) and rate of mild hypoglycemia ($P$ = .015) decreased in the intervention group.[65] After 31 months of follow-up, the rate of severe hypoglycemia from baseline was reduced by 0.6 events/patient-year in the intervention group and by 0.5 events/patient-year in the control group ($P$ = .042). Fewer patients in the intervention group experienced at least 1 severe hypoglycemic episode versus the control group (12.5% vs 26.5%, respectively; $P$ = .04).[64]

## Summary

Hypoglycemia is a common occurrence in patients with DM that may be caused by several factors. Insulin and secretagogues confer the highest risk of hypoglycemia among current pharmacologic treatment options; some investigational agents are associated with lower rates of hypoglycemia. To improve DM-related outcomes, including reducing the risk and consequences of hypoglycemia, effective patient self-management is essential. Physician-patient collaboration is vital to develop and modify a treatment plan acceptable to the patient. Educational programs are available to help patients improve blood glucose awareness and overall hypoglycemia prevention and management. Empowering patients with education, tools, awareness, and an individualized plan of treatment is recommended with the goal of decreasing the frequency and severity of hypoglycemic episodes, as well as improving quality of life and health outcomes. ■

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