Preventing and Managing Hypoglycemia in Patients with Diabetes

(full update August 2024)

Hypoglycemia is a serious concern in patients with diabetes. Hypoglycemia can cause irreversible cognitive impairment, dementia, falls, vehicular accidents, other injuries, and death.[1] The table below addresses common clinical questions about hypoglycemia in patients with diabetes.

Clinical Question	Suggested Approach or Resource

Which patients are at highest risk of hypoglycemia[a]?	• Major risk factors (i.e., those posing high risk of level 2 or 3 hypoglycemia[a]) for patients receiving insulin or secretogogues[d] (per ADA).[28]
	  ○ level 2 or 3 hypoglycemia episode within the past three to six months*
	  ○ intensive insulin therapy
	  ○ hypoglycemia unawareness
	  ○ end-stage kidney disease
	  ○ cognitive impairment
	  ○ socioeconomic factors (food insecurity, low income, homelessness, religious fasting)
	• Major risk factors for level 3 hypoglycemia[a] for patients receiving insulin or sulfonylureas (per Diabetes Canada): history of severe hypoglycemia[a], hypoglycemia unawareness, older age/frailty, low (<7%) or high A1c, long duration of insulin use or diabetes, neuropathy, adolescent, pregnancy, preschool age, cognitive impairment, low health literacy, low economic status/food insecurity, chronic kidney disease[24]
	• Other risk factors (per ADA):
	  ○ Multiple recent episodes of level 1 hypoglycemia[a], basal insulin use, age ≥75 years, female, variable glycemic control, multiple medications, cardiovascular or chronic kidney disease, neuropathy, retinopathy, depression, low health literacy, substance use disorder[28]
	• Certain medications may affect perception or response to hypoglycemia:[7]
	  ○ Beta-blockers, especially noncardioselective agents: may blunt adrenergic symptoms (e.g., anxiety, palpitations, sweating, shaking) and impair counterregulatory response.[7] Patients can still feel faint, dizzy, confused, sleepy, weak or irritable, or have problems with speech or vision.[2,7] They might also have a headache.[2]
	  ○ SSRIs (may alter perception of hypoglycemic symptoms)[7]

What are the symptoms of hypoglycemia?	• Symptoms can be classified as autonomic (neurogenic) or neuroglycopenic.[2]
	  ○ Autonomic: shakiness, tachycardia, sweating, anxiety, hunger, nausea, tingling
	  ○ Neuroglycopenic: difficulty concentrating or speaking, confusion, weakness, dizziness, drowsiness, headache, vision changes

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Do analog insulins pose a lower risk of hypoglycemia?	• Basal analogs pose a lower risk of hypoglycemia than NPH insulin. Insulin degludec and insulin glargine 300 units/mL pose a lower risk of hypoglycemia than insulin glargine 100 units/mL or insulin determir.[24] • Rapid-acting analogs are preferred over regular insulin to reduce hypoglycemic risk in patients with type 1 diabetes.[27]
What resources are available to help educate patients about hypoglycemia?	From the American Diabetes Association: o Understanding and Managing Low Blood Glucose (Hypoglycemia): https://diabetes.org/living-with-diabetes/treatment-care/hypoglycemia From Diabetes Canada: o Hypoglycemia Low Blood Sugar in Adults: https://www.diabetes.ca/diabetescanadawebsite/media/managing-my-diabetes/tools%20and%20resources/hypoglycemia-low-blood-sugar-in-adults.pdf?ext=.pdf
How can hypoglycemia be prevented?	• Patients should be educated to manage situations that put them at risk of hypoglycemia: fasting, delayed meals, alcohol use, exercise, or sleep.[28] For example: o Patients should be educated about adjusting insulin and/or secretagogue[d] use and carbohydrate intake for exercise.[1] o Patients on intensive insulin should periodically check nighttime fingersticks at a time corresponding to peak overnight insulin effect, to identify need for regimen change.[2] • Ask about any hypoglycemic episodes at each visit.[28] • Individualize glycemic targets o Choose a preprandial glucose target that balances glycemic control and risk of hypoglycemia: 80 to 130 mg/dL (4.4 to 7.2 mmol/L) [Evidence level B-3].[28] o An A1c goal of <7% may not be appropriate for patients with recurrent or severe hypoglycemia,[a] especially older adults treated with insulin or a secretagogue.[d,24,28] Consider a goal of <8% (ADA) or ≤.8.5%) for such patients.[11,28] • Re-think the treatment regimen if the patient experiences hypoglycemia unawareness, recurrent hypoglycemia, or level 2 or 3 hypoglycemia.[a,24,28] • Use agents other than insulin or a secretagogue[d] for type 2 diabetes when possible.[24] • For patients with hypoglycemia unawareness, target glucose should be increased to avoid hypoglycemia for several weeks to three months to help restore awareness.[24,28] • Prescribers, the patient, and caregivers should monitor cognitive function.[28] • Consider continuous glucose monitoring for insulin-treated patients and others at high risk for hypoglycemia.[24,28] • Be watchful for medications that might cause hypoglycemia (e.g., quinolones, tramadol).[15,16]
What is the general approach to treatment of hypoglycemia? *Continued…*	• If the patient is **conscious**, give glucose 15 to 20 g (20 g if severe[a]) if blood glucose <70 mg/dL (3.9 mmol/L).[24,28] See **footnote b** for glucose source examples. Repeat glucose 15 g in 15 minutes if blood glucose still <70 mg/dL (3.9 mmol/L).[24,28]

Clinical Question	Suggested Approach or Resource
What is the general approach to treatment of hypoglycemia, continued	• If the patient is **unconscious**, or unwilling to cooperate with oral intake, give **glucagon** IM, SC, IV, or intranasal (route of administration is product-specific [see below]).[24,28] If **intravenous access is available**, 20 to 50 mL of D50W (i.e., 10 to 25 g of glucose) over one to three minutes can be given.[24] o It may take five to 15 minutes for the patient to regain consciousness after glucagon administration.[4] Turn the patient on their side; they may vomit.[4,6] Call emergency services (911).[6,9] Glucagon may be repeated in 15 minutes while waiting for emergency help.[6] • Once hypoglycemia is reversed, the patient should eat their usual meal, or snack if the usual mealtime is >1 hour away.[24] The snack should consist of carbohydrate (15 g) plus protein (e.g., seven crackers plus a piece of cheese, or a slice of bread plus two tablespoons of peanut butter).[2,5] • Patients taking acarbose or miglitol (*Glyset*, US) must use oral glucose (one tablespoon honey or one cup non-fat milk if unavailable) or glucagon.[2,3,13]
Which patients should have a glucagon product on hand?	• All patients using insulin or those with one major risk factor or multiple other risk factors for hypoglycemia (Canada: patients using insulin or at risk of level 3 hypoglycemia[a]) should have unexpired glucagon or dasiglucagon (*Zegalogue*; US only) on hand.[24,28] o The patient's caregiver or frequent contacts (e.g., family, friends, school personnel, roommate, coworker, correctional officer) should be told where it is and how to use it.[24,28]
How should glucagon products be stored?	*Baqsimi* • Keep *Baqsimi* in its shrink-wrapped tube to protect it from moisture.[9,19] • Avoid storing where the temperature may exceed 86ºF (30ºC).[9,19] *Baqsimi* has a 24-month shelf-life from date of manufacture.[8,21] Glucagon emergency kit (glucagon powder; requires reconstitution with included diluent) • Store at 68ºF to 77ºF (20ºC to 25ºC), with excursions to 15ºC to 30ºC (59ºF to 86ºF) allowed (i.e., USP controlled room temperature).[29,30] • Fresenius Kabi (US) product may be stored for up to 24 months (or up to expiration date, whichever is first) in original packaging to protect from light.[29] *Gvoke HypoPen*, *Gvoke PFS*, or *Gyoke* kit (vial and syringe)(US) • Store at 68ºF to 77ºF (20ºC to 25ºC), with excursions to 15ºC to 30ºC (59ºF to 86ºF) allowed.[17] Store *Gvoke HypoPen* and *Gvoke PFS* in the sealed pouch.[17] *Gvoke HypoPen* shelf-life is ≤24 months from date of manufacture for the pen for children 2 to <12 years of age, and ≤30 months for the pen for patients ≥12 years of age.[20] *Zegalogue* prefilled syringe, *Zegalogue* autoinjector (US) • Store in refrigerator (36°F to 46°F [2°C to 8°C]). May be stored for up to 12 months at room temperature between 68°F and 77°F (20°C and 25°C). Do not return *Zegalogue* to the refrigerator once it has been removed.[22] • Store in protective case provided and protect from light.[22]

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How do newer glucagon products compare to traditional glucagon kits?	**Ease of use** • **Traditional glucagon kits** provide a powder that requires dilution with a syringe and needle to add diluent. o The dose must be drawn up into the syringe and injected IM or SC in the upper arm, thigh, or buttocks, or IV.[29,30] o Fresenius product (US): half the usual dose (i.e., 0.5 mg instead of 1 mg) must be given to children <25 kg (or if weight unknown and <6 years of age).[29] Amphastar generic: dose is 0.5 mg (or 20 to 30 mcg/kg) for children weighing <20 kg.[30] • **Autoinjectors (US only)** o ***Gvoke HypoPen*** is a prefilled autoinjector for SC administration.[17] ▪ Administered by pushing the autoinjector down on the skin of the lower abdomen, outer thigh, or outer upper arm for five seconds.[17] A window on the injector turns red when the dose has been administered.[17] ▪ Available in two strengths: 1 mg and 0.5 mg.[17] The dose is 1 mg for patients ≥12 years of age and for patients 2 to <12 years of age who weigh ≥45 kg.[17] The dose for patients <45 kg who are 2 to <12 years of age is 0.5 mg.[17] o ***Zegalogue*** is available as a prefilled autoinjector for SC administration.[22] ▪ Administered by pushing the autoinjector down on the skin of the lower abdomen, buttocks, front or back of thigh, or outer upper arm until the yellow needle guard is fully pressed down (there may be a click) and holding for ten seconds.[22] A window on the injector turns red when the dose has been administered.[22] ▪ The dose (0.6 mg) is the same for all patients ≥6 years of age.[22] • **Prefilled syringes (US only)** o ***Gvoke PFS*** is a prefilled syringe for SC administration.[17] ▪ Administered by removing the cap, pinching the skin at the injections site (lower abdomen, outer thigh, outer upper arm), inserting the needle into the skin at a 90º angle, and pushing the plunger.[17] ▪ Available in two strengths: 1 mg and 0.5 mg.[17] The dose is 1 mg for patients ≥12 years of age and for patients 2 to <12 years of age who weigh ≥45 kg.[17] The dose for patients <45 kg who are 2 to <12 years of age is 0.5 mg.[17] o ***Zegalogue*** is available as a prefilled syringe for SC administration.[22] ▪ Administered by removing the cap, pinching the skin at the injection site (lower abdomen, buttocks, front or back of the thigh, or outer upper arm), inserting the needle into the skin at a 45° angle, and pushing the plunger.[22] ▪ The dose (0.6 mg) is the same for all patients ≥6 years of age.[22] o ***Baqsimi*** is a single-use, ready-to-use intranasal powder.[9,19] ▪ Administered by inserting the device tip into one nostril, then depressing the plunger until the green line on the plunger is no longer visible.[9,19] ▪ Inhaling is not required.[9,19] Nasal congestion or decongestant use does not affect absorption.[9,19]
Continued…	

Clinical Question	Suggested Approach or Resource
Newer products vs traditional glucagon injection, continued	▪ The dose (3 mg) is the same for all patients ≥4 years of age.[9,19] ▪ A demo product is available for US prescribers. Contact Eli Lilly at 800-545-5979. **Cost**[c] • **US:** *Gvoke HypoPen* ($316.04), *Gvoke PFS* ($316.04), *Baqsimi* ($289.20), *Zegalogue* ($309), glucagon emergency kit (~$280). *Gvoke PFS*, *Gvoke HypoPen*, *Baqsimi*, and *Zegalogue* are available in a two-pack. • **Canada**: *Baqsimi* ($166.37). The Amphastar US glucagon product has "designated drug" status in Canada at least through 2024.[31] No Canadian cost was available at time of writing. **Efficacy** • There are no head-to-head studies of *Baqsimi*, *Gvoke* (US), and *Zegalogue* (US).[23] • Time to administer *Baqsimi*, *Gvoke*, and *Zegalogue* is faster than for traditional glucagon products.[23] Administration errors are likely with traditional IM injection (e.g., incomplete reconstitution or injection, injection of diluent alone, bent needle, etc).[10,18] • *Baqsimi* may work faster than *Gvoke*.[23] • In adults, traditional IM glucagon seems to raise blood glucose to above 70 mg/dL (4 mmol/L) by about four minutes faster than *Baqsimi* or *Gvoke*, but this can be offset by the time it takes to prepare injectable glucagon.[10,17,18] In children <12 years of age, *Baqsimi* is about as fast as IM glucagon.[9,19] In adults, the time to glucose recovery is similar with *Zegalogue* (~10 minutes) and traditional IM glucagon (~12 minutes).[22] • The maximum blood glucose achieved with *Baqsimi* may be lower than with *Gvoke* or Zegalogue, with lower risk of rebound hyperglycemia than traditional glucagon injection.[23] **Tolerability** • Glucagon commonly causes nausea, vomiting, headache, and injection site reactions.[13] • *Baqsimi* nasal spray can also cause red, watery, and/or itchy eyes; stuffy, itchy, and/or runny nose; sneezing; and itchy throat.[9,19] • In a systematic review, there was a nonsignificant trend suggesting better tolerability with *Baqsimi* vs *Gvoke* or *Zegalogue*.[23]

Abbreviations: ADA = American Diabetes Association; IM = intramuscular; SC = subcutaneous

a. **SEVERITY OF HYPOGLYCEMIA**

American Diabetes Association[28]	**Diabetes Canada**[24]
Level 1: glucose <70 mg/dL (4 mmol/L) but ≥54 mg/dL (3 mmol/L). Considered clinically important, even if asymptomatic.	Autonomic symptoms present, without mental status changes. Glucose typically 3 to 3.9 mmol/L.
Level 2: glucose <54 mg/dL (3 mmol/L)	Neuroglycopenic symptoms present but without significant mental status changes. Autonomic symptoms may or may not be present. Glucose level typically <3 mmol/L.
Level 3: severe episode with impaired mental or physical function requiring assistance. Risk of seizures, unconsciousness, and death.	Neuroglycopenic symptoms present with significantly impaired mental or physical function. Patient requires assistance to treat.

b. **Glucose sources (15 g)**: [2,4,5,12,14]
- glucose tablets (usually 4 tablets; check label)
- 1 heaping tablespoon (3 packets) of table sugar
- 5 sugar cubes
- Raisins (2 tablespoons)
- 1/2 to 2/3 cup (~120 to 150 mL) of fruit juice or regular (non-diet) soft drink
- 6 *Life Savers*
- 1 tablespoon (15 mL) of honey or corn syrup

c. Cost is wholesale acquisition cost (WAC). US medication pricing by Elsevier, accessed August 2024.
d. Secretogogue = sulfonylurea or meglitinide (nateglinide, repaglinide)

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician 2004;69:548-56. https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html.]

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