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November 2019 ~ Resource #351108

Preventing and Managing Hypoglycemia in Patients with Diabetes

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. Educate patients with our patient handout, *How To Handle Low Blood Sugar*.

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

Clinical Question	Suggested Approach or Resource
Which patients are at highest risk of hypoglycemia[a]?	Patients with Type 1 diabetes (highest risk) • Risk factors for severe hypoglycemia[a] include prior episode of severe hypoglycemia, A1C <6%, hypoglycemic unawareness, long duration of diabetes, autonomic neuropathy, younger age (i.e., too young to recognize and self-treat mild hypoglycemia, or adolescent),[2] intensive glycemic control[14] Patients with type 2 diabetes using insulin or **sulfonylurea** (lower risk), especially with: • severe cognitive impairment, older age, low health literacy, food insecurity, poor glycemic control, hypoglycemic unawareness, long duration of insulin therapy, chronic kidney disease, or neuropathy,[2] intensive glycemic control,[14] bariatric surgery 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)
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
Do analog insulins pose a lower risk of hypoglycemia?	See our chart, *Insulin Analogs vs Human Insulin*.

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Clinical Question	Suggested Approach or Resource
What resources are available to help educate patients about hypoglycemia?	From the American Diabetes Association: • Hypoglycemia (Low Blood Sugar): https://www.diabetes.org/diabetes/medication-management/blood-glucose-testing-and-control/hypoglycemia From Diabetes Canada: • 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.[1] For example:
	  • Patients should be educated about adjusting insulin use and carbohydrate intake for exercise.[1]
	  • 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]
	• In at-risk patients, ask about hypoglycemia at each visit.[1]
	• 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].[1,3]
	• Re-think the treatment regimen if the patient experiences hypoglycemia unawareness or level 3 hypoglycemia.[a,1]
	• For insulin-treated patients with hypoglycemia unawareness, or an episode of level 2 hypoglycemia,[a] target glucose should be increased to avoid hypoglycemia for several weeks to three months to help restore awareness.[1,2]
	• Prescribers, the patient, and caregivers should monitor cognitive function.[1]
	• Consider continuous glucose monitoring for appropriate patients.
	• Be watchful for medications that might cause hypoglycemia (e.g., quinolones, tramadol).[15,16]

What is the general approach to treatment of hypoglycemia?	• If the patient is **conscious**, give glucose 15 to 20 g (20 g if severe[a]) if blood glucose <70 mg/dL (4 mmol/L).[1,2] See **footnote b** for glucose source examples. Repeat glucose 15 g in 15 minutes if blood glucose still <70 mg/dL (4 mmol/L).[1,2] • If the patient is **unconscious**, or unwilling to cooperate with oral intake, give **glucagon**.[1,2] If **intravenous access is available**, give 20 to 50 mL of D50W (i.e., 10 to 25 g of glucose) over one to three minutes.[2] • 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 911.[8,9] Glucagon may be repeated while waiting for emergency help.[8] • Once hypoglycemia is reversed, the patient should eat their usual meal, or snack if the usual mealtime is >1 hour away.[2] The snack should consist of 15 g carbohydrate 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 (*Precose* [U.S.], *Glucobay* [Canada]) or miglitol (*Glycet*, Canada) must use glucose tablets, one cup of non-fat milk, or one tablespoon honey.[2,13]

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Clinical Question	Suggested Approach or Resource
Which patients should have a glucagon product on hand?	• All patients at risk of level 2 hypoglycemia[a] should have unexpired glucagon or dasiglucagon (U.S. only) on hand (Note: dasiglucagon is NOT included in guideline recommendations, as it was FDA-approved approved after publication).[1,22] • 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.[1,4,22]
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.[21] *GlucaGen Hypokit* • **U.S.**: may be stored for up to 24 months (or up to expiration date, whichever is first) where temperature does not exceed 77ºF (25ºC).[8] Protect from light by keeping in original packaging.[8] • **Canada**: store in refrigerator (2ºC to 8ºC). Patient may store up to 18 months (or up to expiration date, whichever is first), where temperature does not exceed 25ºC.[11] Keep from freezing.[11] Keep in sealed packing. Protect from light.[11] *Gvoke HypoPen* or *Gvoke PFS* (U.S.) • Store in sealed pouch at 68ºC to 77ºC.[17] *Gvoke* shelf-life will be ≤24 months from date of manufacture.[20] *Zegalogue* (U.S.) • 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] • Protect from light by keeping in original packaging.[22]
How do newer glucagon products compare to traditional glucagon injection? *Continued…*	Ease of use • **Traditional glucagon kits** provide a powder that requires dilution with a syringe and needle to add diluent. The dose must be drawn up into the syringe and injected in the arm or outer mid-thigh, IM or SC.[2,4,6,8] 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 [Canada, <6 to 8 years]).[8,11] • ***Gvoke HypoPen*** is a prefilled autoinjector for SC administration.[17] It is 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] ***Gvoke PFS*** is a traditional prefilled syringe for SC administration.[17] It is administered by removing the cap, pinching the skin at the injection site, inserting the needle into the skin at a 90º angle, and pushing the plunger.[17] • Both the autoinjector and the prefilled syringe are 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]

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Clinical Question	Suggested Approach or Resource

Newer products vs traditional glucagon injection, continued	• ***Baqsimi*** is a single-use, ready-to-use intranasal powder.[9,19] The dose is the same for all patients ≥4 years of age.[9,19]
	  • It is 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]
	  • A demo product is available for U.S. prescribers. Contact Eli Lilly at 800-545-5979.
	• ***Zegalogue*** comes as a single-dose prefilled syringe and a single-dose prefilled autoinjector for SC administration.[22]
	  • The dose (0.6 mg) is the same for all patients ≥6 years of age.[22]
	  • Either product is administered SC in the lower abdomen, buttocks, front or back of the thigh, or outer upper arm.[22]
	  ▪ **Prefilled syringe** is administered by removing the cap, pinching the skin at the injection site, inserting the needle into the skin at a 45° angle, and pushing the plunger.[22]
	  ▪ **Autoinjector** is administered by pushing the autoinjector down on the skin 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]
	Cost
	• U.S. cost is about the same for *GlucaGen HypoKit*, *Gvoke HypoPen*, *Gvoke PFS*, or *Baqsimi* (~$280[c]) and slightly higher for *Zegalogue* (~$310[c]). *Gvoke*, *Baqsimi*, and *Zegalogue* are available in a two-pack. (Canadian *Baqsimi* cost is not available at time of publication.)
	Efficacy
	• In adults, traditional IM glucagon seems to raise blood glucose above 70 mg/dL (4 mmol/L) by about four minutes faster than *Baqsimi*, but this can be offset by the time it takes to prepare injectable glucagon.[10] Plus, administration errors are likely with the traditional IM injection (e.g., incomplete reconstitution or injection, injection of diluent alone, bent needle, etc).[10,18] In children <12 years of age, *Baqsimi* is about as fast as IM glucagon.[9,19]
	• In adults, traditional IM glucagon seems to raise blood glucose above 70 mg/dL (4 mmol/L) by about four minutes faster than *Gvoke*.[17] But errors are more likely with traditional IM glucagon, and *Gvoke* is faster to use.[18]
	• In adults, the time to glucose recovery seems similar with traditional IM glucagon (~12 minutes) and *Zegalogue* (~10 minutes).[22]
	Tolerability
	• *Baqsimi* can cause nausea (~30%) and vomiting (~15%), like injectable glucagon.[8,9,19] Other common side effects include red, watery, and/or itchy eyes; stuffy, itchy, and/or runny nose; sneezing; and itchy throat.[9,19]
	• In adults, adverse effects associated with *Gvoke* include nausea (30%), vomiting (16%), and injection site reactions (7%).[17]
	• *Zegalogue* can cause nausea (~60%), vomiting (25% to 50%), headache (~10%), diarrhea (~5%), and injection-site reactions (≤5%).[22]

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a. **SEVERITY OF HYPOGLYCEMIA**

American Diabetes Association[1]	**Diabetes Canada**[2]
Level 1: glucose <70 mg/dL (4 mmol/L) but ≥54 mg/dL (3 mmol/L). Considered clinically important, even if asymptomatic.	Mild: autonomic (neurogenic) symptoms present. Patient can self-treat.
Level 2: glucose <54 mg/dL (3 mmol/L]	Moderate: autonomic (neurogenic) and neuroglycopenic symptoms present, but patient can self-treat.
Level 3: severe episode with impaired mental or physical function requiring assistance. Risk of seizures, unconsciousness, and death.	Severe: patient requires assistance. Loss of consciousness may occur. Glucose usually <2.8 mmol/L (50 mg/dL).

b. **Glucose sources (15 g)**:[2,4,5,12,13,14]

- glucose tablets (3 to 4 tablets)
- 1 heaping tablespoon (3 packets) of table sugar
- 5 sugar cubes
- Raisins (2 tablespoons)
- 1/2 cup of fruit juice or regular (non-diet) soft drink
- 6 *Life Savers*
- 1 tablespoon (15 mL) of honey, syrup, or corn syrup

c. Cost is wholesale acquisition cost (WAC). Medication pricing by Elsevier, accessed May 2021.

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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 RCT 2. 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).
RCT = randomized controlled trial; **SR** = systematic review
[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. http://www.aafp.org/afp/2004/0201/p548.pdf.]

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Cite this document as follows: **Clinical Resource,** ***Preventing and Managing Hypoglycemia in Patients with Diabetes. Pharmacist's Letter/Prescriber's Letter.*** **November 2019.**

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