QUESTION

Should glucagon preparations that do not have to be reconstituted vs. preparations that do have to be reconstituted be used for people with severe hypoglycemia?

POPULATION:	people with severe hypoglycemia
INTERVENTION:	glucagon preparations that do not have to be reconstituted
COMPARISON:	preparations that do have to be reconstituted
MAIN OUTCOMES:	Recovery from hypoglycemia: Increase in plasma glucose to ≥ 70 mg/dL or increase of ≥ 20 mg/dL from glucose nadir ; Clearance of neuroglycopenic symptoms; Time to glycemic recovery (in minutes); Autonomic adverse events; Cardiovascular adverse events; Adverse events related to the ear; Gastrointestinal adverse events; Headache; Nasal adverse events; Nausea; Ophtalmologic adverse events; Adverse events related to the throat; Total adverse events; Vomiting; Ease of education for patient and family;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective
BACKGROUND:	Severe hypoglycemia is a common acute complication of insulin therapy in patients with type 1 and type 2 diabetes mellitus. Sulphonylureas and glinides used for treatment of type 2 diabetes can also cause severe hypoglycemia. Prolonged severe hypoglycemia is associated with neurological and cardiovascular complications and may cause coma and death. Injectable glucagon can rapidly reverse hypoglycemia; however, prior to the advent of nasal and stable liquid glucagon preparations, glucagon administration required a multistep procedure to reconstitute lyophilized glucagon powder before it is injected. A consequence of this complex administration has led to failure to administer full therapeutic doses in up to half of treated patients. This has often required emergency medical treatment and/or admission to a hospital.
CONFLICT OF INTERESTS:	Endocrine Society conflict of interest management policies were applied and the following panel members were recused as a result of risk of conflicts of interest: Grazia Aleppo Elizabeth Seaquist

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Hypoglycemia and the use of glucagon are priorities for all patients with diabetes who use insulin and for patients with type 2 diabetes treated with sulphonylureas and glinides, as severe hypoglycemia is common, costly and patients often do not have glucagon. Ease of administration is important.** The T1D Exchange reported that 6% of participants surveyed had experienced an episode of severe hypoglycemia-related seizure or loss of consciousness during a 3-month period(1). Severe hypoglycemia (SH) is a frequent cause of emergency department visits (2) and SH events (SHE) impose a substantial economic burden (3) and adversely affect quality of life. SHEs are a common reason to summon emergency medical services and are associated with considerable costs to health care payers (4, 5, 6, 7). Among persons aged 65 years or older, SHEs occur at an estimated rate of 5.01 per 100 person-years. Inpatient admissions for hypoglycemia cost an average of $18,961, and emergency department visits cost an average of $1,487, and yet few patients with diabetes receive a prescription for glucagon (8). Children and adolescents with diabetes spend many hours at school or day care centers and in many states only school nurses or other trained health professionals are allowed to administer glucagon (9, 10, 11). If a school nurse is not available when a student is experiencing SH, the only recourse may be to summon emergency medical help, which delays treatment.	This problem is a priority especially since there are newer, simpler, and easy to use treatments available

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		Panel discussed that there was non-inferiority between the two types of glucagon preparations, with trivial differences in desirable effects. Non-inferiority is only relevant once the glucagon is given.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)

				Risk with glucagon preparations that do have to be reconstituted (i.e. available as a powder or diluent)	Risk difference with glucagon preparations that do not have to be reconstituted
Recovery from hypoglycemia: Increase in plasma glucose to ≥ 70 mg/dL or increase of ≥ 20 mg/dL from glucose nadir follow up: 30 minutes	655 (5 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	**OR 0.82** (0.18 to 3.66)	Study population	
				1,000 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Ease of education for patient and family - not reported	-	-	-	**-**	**-**
Clearance of neuroglycopenic symptoms follow up: 30 minutes	154 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,d]	**OR 0.48** (0.04 to 5.41)	Study population	
				987 per 1,000	**14 fewer per 1,000** (232 fewer to 10 more)
Time to glycemic recovery (in minutes) follow up: 3 hours	726 (4 RCTs)	⨁⨁◯◯ LOW [b,e]	-	The mean time to glycemic recovery (in minutes) was **0** minutes	MD **2.22 minutes more** (1.09 more to 3.36 more)
Autonomic adverse events follow up: 2 hours	0 (2 RCTs)	⨁◯◯◯ VERY LOW [b,f,g]	-	We did not find a significant difference between groups (n=294; IRR = 0.43; 95% CI: 0.06 to 2.91; I2= 0.00%)	
Cardiovascular adverse events follow up: 2 hours	0 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,f]	-	We did not find a significant difference between groups (n=141; IRR = 8.87; 95% CI: 0.48 to 164.81; I2= N/A)	
Adverse events related to the ear follow up: 2 hours	0 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,f]	-	We did not find a significant difference between groups (n=141; IRR = 4.93; 95% CI: 0.24 to 102.68; I2= N/A)	
Gastrointestinal adverse events follow up: 3 hours	0 (2 RCTs)	⨁◯◯◯ VERY LOW [b,g,h]	-	We did not find a significant difference between groups (n=237; IRR = 0.80; 95% CI: 0.53 to 1.19; I2= 0.00%)	
Headache follow up: 3 hours	0 (3 RCTs)	⨁⨁◯◯ LOW [b,i]	-	There were more events in the intervention group (n=378; IRR = 2.19; 95% CI: 1.10 to 4.37; I2= 0.00%).	

Delay in effective treatment is the most important difference for the usual care.

Nasal adverse events follow up: 3 hours	0 (3 RCTs)	⨁⨁◯◯ LOW [b,i]	-	There were more events in the intervention group (n=378; IRR = 5.51; 95% CI: 1.91 to 15.90; I2=0.00%).
Nausea follow up: 9 weeks	0 (2 RCTs)	⨁◯◯◯ VERY LOW [b,f,g]	-	We did not find a significant difference between groups (n=303; IRR = 1.00; 95% CI: 0.61 to 1.62; I2=37.00%)
Ophtalmologic adverse events follow up: 3 hours	0 (3 RCTs)	⨁⨁◯◯ LOW [b]	-	There were more events in the intervention group (n=378; IRR = 6.21; 95% CI: 1.84 to 20.91; I2= 0.00%)
Adverse events related to the throat follow up: 2 hours	0 (2 RCTs)	⨁◯◯◯ VERY LOW [b,g,i]	-	We did not find a significant difference between groups (n=284; IRR = 3.87; 95% CI: 0.43 to 35.05; I2= 0.00%).
Total adverse events follow up: 3 hours	0 (2 RCTs)	⨁◯◯◯ VERY LOW [b,c,i]	-	We did not find a significant difference between groups (n=205; IRR = 1.06; 95% CI: 0.45 to 2.52; I2= 73.00%)
Vomiting follow up: 9 weeks	0 (2 RCTs)	⨁◯◯◯ VERY LOW [b,f,g]	-	We did not find a significant difference between groups (n=303; IRR = 1.54; 95% CI: 0.70 to 3.40; I2= 11.00%)

a. Serious concerns about conflicts of interest in 4 trials.
b. Serious concerns about indirectness due to patients being induced with hypoglycemia.
c. Very serious concerns about imprecision due to very wide CI that has appreciable benefits and harms.
d. Serious concerns about lack of allocation concealment and possible conflicts of interest.
e. Serious concerns about lack of allocation concealment and possible conflicts of interest in 3 trials.
f. One trial with serious concerns about possible conflicts of interest
g. Wide CI that has appreciable benefits and harms.
h. One trial with serious concerns about the process of random sequence generation.
i. Two trials at high risk of bias.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ○ Small
- ● Trivial
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with glucagon preparations that do have to be reconstituted (i.e. available as a powder or diluent)	Risk difference with glucagon preparations that do not have to be reconstituted
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ADDITIONAL CONSIDERATIONS

Ophthalmologic adverse events described in the studies were mostly mild.

Panel discussed that nasal glucagon dosage is higher (3 mg vs 1 mg for injectable glucagon), which may explain the difference in some side effects. Also, the route of administration explains the nasal and ophthalmologic adverse events.

				1,000 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Ease of education for patient and family - not reported	-	-	-	**-**	**-**
Clearance of neuroglycopenic symptoms follow up: 30 minutes	154 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,d]	**OR 0.48** (0.04 to 5.41)	Study population	
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Headache follow up: 3 hours	0 (3 RCTs)	⨁⨁◯◯ LOW [b,i]	-	There were more events in the intervention group (n=378; IRR = 2.19; 95% CI: 1.10 to 4.37; I2= 0.00%).	
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Total adverse events follow up: 3 hours	0 (2 RCTs)	⨁◯◯◯ VERY LOW [b,c,i]	-	We did not find a significant difference between groups (n=205; IRR = 1.06; 95% CI: 0.45 to 2.52; I2= 73.00%)
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i. Two trials at high risk of bias.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		Studies were done in a controlled clinical setting in which mild to moderate hypoglycemia was induced and glucagon was administered by a nurse, which is an indirect setting for outpatient use. The panel noted that this setting would not be representative of the real world in which severe hypoglycemia necessitating glucagon administration occurs spontaneously and often occurs during the night. Glucagon is typically administered by a non-trained family member or other third party in a stressful, high anxiety state.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	**Hypoglycemia is a major concern for patients and their family members. They would place a high value on an easy to use and reliable method of treating severe hypoglycemia.** More than 60% of family members of people with diabetes are worried about the risk of hypoglycemic events (12). During SH episodes, people with diabetes depend on others to help with treatment. This occurs in a state of fear, stress and high anxiety when the person with diabetes is experiencing a seizure or is unconscious.	Unlikely to be differences for having available an easy to use and reliable treatment for severe hypoglycemia.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Based on clinical outcomes from the included studies, based on very low certainty evidence.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Glucagon can be costly especially for the uninsured or underinsured. However there do not appear to be significant differences in cost between the currently available forms of glucagon.** Each dose costs about ~$337 without insurance. The mean costs of hospital admission for serious hypoglycemia is $17,564 in the US according to Quilliam et al. (Am J Manag Care. 2011;17(10): 673-680.) This is for type 2 diabetes. (28). Type 2 DM is the most common experiencing SH episodes. The cost of glucagon depends on whether the person with diabetes has insurance and whether the prescription is renewed. The average wholesale price (AWP), a benchmark for the cost of a particular drug, for the various glucagon preparations available in the USA, is shown in the Table. Glucagon Emergency Kit, Eli Lilly — 1 mg — $336.96 GlucaGen Hypokit, NovoNordisk — 1 mg — $351.66 Baqsimi, Eli Lilly — 3 mg — $336.96 Baqsimi 2-pack, Eli Lilly — 3 mg — $673.92 Gvoke PFS 1-pack, Xeris Pharmaceuticals — 0.5 mg per 0.1 mL — $336.96 Gvoke PFS 1-pack, Xeris Pharmaceuticals — 1 mg per 0.2 mL — $336.96 Gvoke Hypopen 2-pack, Xeris Pharmaceuticals — 0.5 mg per 0.1 mL — $673.92 Gvoke Hypopen 2-pack, Xeris Pharmaceuticals — 1 mg per 0.2 mL — $673.92 Source: AmerisourceBergen Corporation (n.d.) *Drug Catalog*. ABC Order. https://abcorder.americourcebergen.com Accessed February 15, 2021	Panel discussed that newer preparations have been priced nearly identical to the preparations that need to be reconstituted. Cost differences in the different formulations of glucagon are negligible. Rescue from severe hypoglycemia with all available glucagon formulations is likely to have comparable and considerable cost savings for overall resource use (cost of summoning an EMT, transport via ambulance to an emergency department, evaluation, and treatment in an emergency department). The panel considered that preparations that need to be reconstituted may result in failure of proper administration and result in downstream costs for required EMS (some of which don't have glucagon). There were no studies currently reporting on these overall costs, to determine the magnitude of savings with nasal glucagon.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**There is limited data evaluating the cost-effectiveness of both stable liquid glucagon and intranasal glucagon vs IM glucagon requiring reconstitution, suggesting that these newer forms of glucagon may be cost-effective.** The economic impact of the usability advantage of intranasal (IN) glucagon over IM glucagon was explored in cost offset and budget impact analyses in the US setting for T1D and T2D patients treated with basal-bolus regimens. Reduced spending resulted from reduced professional emergency services utilization as successful treatment was more likely with IN glucagon and has the potential to decrease costs associated with treatment of SH (13). A modeling study assessed the annual value of a ready-to-use, room-temperature stable liquid glucagon rescue pen and prefilled syringe for treatment of SHEs versus current lyophilized powder glucagon emergency kits (GEK) (14). Ready-to-use liquid gluacgon comes in a prefilled auto-injector designed to promptly administer concentrated liquid glucagon in a simple two-step process. To estimate the economic impact of ready-to-use liquid glucagon, Leinwand et al. developed a one-year budget impact model from a US commercial health plan perspective. Costs for 1 million covered lives were $8.2 million following the introduction of ready-to-use liquid glucagon formatulations compared to almost $9 million before these formluations were available (14).	The included studies were modelling studies. Enhanced usability of new glucagon preparations suggests that they will be used more often than the glucagon emergency kit. If this proves to be true, there will be fewer calls to 911 and fewer ER visits, which would be expected to be cost-effective.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No research evidence identified	The panel highlighted several issues for considering impact on health equity, deciding on a judgement of don't know: 1. Comparing the impact on health equity for use of newer glucagon preparations versus glucagon preparations that do not have to be reconstituted. 2. Given that glucagon preparations that do not have to be reconstituted are new, they may not yet be included on formularies. Highlighted coverage under Medicare. 3. Increased access/not needing to refill with longer expiration date for newer glucagon preparations.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**There is evidence to suggest that the intervention is acceptable to patients and caregivers.** Patients with T1D often **do not fill their prescriptions for a GEK** (15). Those who do have fewer emergency department visits (15). 11% of people with T1D (and 3.5% with T2D) filled a glucagon prescription *after* an emergency department visit for hypoglycemia (16). SH treated outside the hospital uses intimidating intramuscular injection of glucagon requires reconstitution immediately prior to injection due to its instability in solution, a multi-step process prone to error or omission. Most without medical training find this daunting, with substantial risk of errors (17) **leading to inadequate delivery and often ER visits**. A single, 3-mg dose of intranasal glucagon (NG) demonstrated real-life effectiveness in treating moderate and severe hypoglycemia in adults with T1D (18). **NG was well tolerated and easy to use.** In all 12 severe hypoglycemia events caregivers were able to manage SH without emergency assistance. Caregivers reported that NG was easy to use (easy to understand kit instructions 91% events); easy to administer (80.5% events). They were able to **administer NG within 30 seconds in 70.4% events and within 1 minute in 92.7% events** and were satisfied with NG use in 94.4% of SHEs. They stated their willingness to carry NG (97.7% events) and agreed that NG was less intimidating than injectable glucagon (100%) (18). Likewise, in a real-world study of NG administration to treat moderate symptomatic hypoglycemic events in children and adolescents, **more than 90% of caregivers reported that NG administration was easy or very easy and were able to administer NG within 30 seconds in 60.6% of events and within 2 minutes in 100%.** Caregivers (96.9%) reported that NG was less intimidating than injectable glucagon, easy to teach to other caregivers and preferable to needle-based delivery for rescue treatment of SH (19). A simulation study using mannikins compared needle-free NG and commercially available injectable glucagon for ease of use by caregivers of people with diabetes and by others in treating simulated episodes of SH. More than 90% of participants delivered full doses of NG, while 13% and 0% of caregivers and acquaintances delivered full doses of injectable glucagon, indicating that NG is easier for nonmedically trained people to administer. Caregivers and acquaintances rated NG easier to use. **More people with diabetes (PWD) preferred that caregivers or acquaintances (friend/family) use NG because it is easier to use, teach and carry; no chance of needle breakage or accidental needle stick.** Thus, NG has the potential to substantially improve treatment for patients experiencing a life-threatening episode of SH. Risk of accidentally injecting insulin during a SHE can also be reduced with NG (20). A human factors validation program evaluated the **glucagon autoinjector** (GAI) versus marketed glucagon emergency kits (GEKs) for managing SH. A simulated-use human factors usability study was conducted with the GAI versus marketed GEKs in 16 participants, including adult caregivers and first responders, experienced with glucagon administration. A summative human factors validation study of the GAI was conducted with 75 volunteers. Participants were (1) trained on the device and procedure or (2) given time to individually read the instructions and familiarize themselves with the device. Participants returned a week later to perform an unaided rescue attempt that simulated rescue of patients with diabetes suffering a hypoglycemia emergency. Participant actions were recorded for critical rescue tasks and use errors. In the usability study, 88% (14) successfully administered a rescue injection using the GAI versus 31% (5) using GEKs ($P < 0.05$). Mean total rescue time of use was 47.9 seconds with the GAI versus 109 seconds with GEKs ($P < 0.05$). In the validation study, 98.7% successfully administered the rescue injection using the GAI. Overall, there were no patterns of differences between trained versus untrained participants, between caregivers versus first responders or between adults versus adolescents. The authors concluded that the GAI and instructional materials can be correctly, safely, and effectively used by intended user (21). Two human factors studies evaluated whether a **stable liquid formulation of glucagon in a prefilled syringe (G-PFS) could be safely and effectively administered** and evaluated the effectiveness of the product label guide and instructions-for-use (IFU). In a formative study, 11 participants received orientation with the prefilled syringe instructional materials and performed a single unaided rescue attempt. In the validation study, 75 adult and adolescent participants received training or familiarized themselves with the G-PFS IFU, Label Guide, and device. All participants returned 1 week later to perform a single unaided rescue attempt of a simulated person with diabetes suffering from an emergency severe hypoglycemic event. The formative study resulted in a 100% success rate across all rescue dose attempts. The validation study resulted in 74/75 (99%) of participants successfully using the G-PFS to administer the full glucagon rescue dose, and validated that intended users could learn from, comprehend, and recall the glucagon prefilled syringe instructions to successfully use the product. The authors concluded that **the G-PFS provides a familiar, easy-to-use alternative to currently marketed lyophilized glucagon kits for treating severe hypoglycemia. The G-PFS IFU and Label Guide enable even untrained users to successfully administer a full rescue dose of stable liquid glucagon** (22)**.**	Nasal or self-injecting glucagon autoinjector: Because glucagon preparations that do not have to be reconstituted are relatively new, patients who see an endocrinologist may have more access to these products compared to patients who receive care from non-specialist clinicians. Patients with Type 1 and some with Type 2 DM may be attuned to new product via social media. Such people may ask and prefer newer, easier to use preparations. There is a question about whether new products will be approved. Panel discussed and noted the shelf-life: Dasiglucagon can be stored at room temperature (68-77 degrees F) for up to 12 months. Should be stored in refrigerator (36-46 degrees F); expires after 3 years when refrigerated. If removed from fridge and stored at room temperature, new expiration date (12 months) must be recorded on protective case. The shelf life of nasal glucagon is up to 24 months from date of manufacture when stored under proper conditions. Does not require refrigeration and can be exposed to temperatures up to 86 degrees F. Nasal glucagon should be kept in its shrink-wrapped packaging until used. The shrink-wrap will keep the drug from being exposed to moisture. The prefilled ready-to-use liquid glucagon pen is stored in sealed foil pouch until use; store at room temp (68-77F); do not refrigerate or freeze. Can be stored in original packaging for up to 2 years from date of manufacture

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**There is evidence to suggest that the intervention (stable liquid and IN glucagon) is feasible to implement.** Despite its well documented safety and efficacy, **glucagon is frequently unavailable** and is underutilized for treatment of SH (23, 24, 25). Studies have also highlighted the **difficulty of using a GEK to treat SH in an actual emergency** (20)**.** Under simulated emergency conditions, 10% of parents of children and adolescents with T1D failed to administer glucagon and 70% of parents reported having trouble with the kit (26). In a more recent simulation study that assessed either caregivers or volunteers (acquaintances) who had been trained on how to use the product, only **13% of caregivers and none of the volunteers were able to correctly administer a full dose and the time to complete the injection was approximately 2 minutes** (20). In simulated emergencies, **GRP and G-PFS demonstrated high functional efficacy: 99% of users successfully administered a full dose of drug as compared with using a GEK that had a very low success rates (6-31%).** The high functional efficacy of GRP and G-PFS significantly reduces user errors and may reduce utilization across emergency medical services (EMS), emergency departments (ED), and inpatient and outpatient costs for SHE. The availability of **nasal glucagon may allow use of glucagon by non-medical school staff, which would avoid delays in administering glucagon to a child experiencing severe hypoglycemia**. The **new glucagon formulations are more likely to be used because they are more user (friends, spouses and others) friendly** to those not used to giving injections or who may have to figure out how to use an auto-injector or powdered NG.	The panel discussed the failure rate of administering glucagon that has to be reconstituted (powder and diluent). People often fail to give all of the glucagon or any of it. New glucagon preparations are available as stable liquid formulations or nasal glucagon. Both stable liquid formulations are available as an autoinjector and prefilled syringe. Because they do not require reconstitution, these products are easier to administer. Successful treatment of severe hypoglycemia, therefore, is more likely to occur but empirical data are currently lacking.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

We recommend glucagon preparations that do not have to be reconstituted over glucagon preparations that do have to be reconstituted (i.e., available as a powder and diluent) be used for outpatients with severe hypoglycemia. (Strong recommendation, very low certainty evidence) (1⊕◯◯◯)

Justification

All the available glucagon formulations have equivalent efficacy and only trivial differences with respect to adverse effects and cost. Ease of use by non-professionally trained users in the life-threatening emergency situation of managing an episode of severe hypoglycemia, which frequently occurs at night, places high value on the intervention that is more feasible to use and has equal cost. The very high rate of failure to administer the correct dose by untrained and even trained persons makes this an exigent issue. The panel issued a strong recommendation based on very low certainty evidence, considering the situation of an episode of severe hypoglycemia to be life-threatening.

Subgroup considerations

None

Implementation considerations

The panel highlighted implementation considerations for children and dosing: Nasal glucagon is approved for age 4 and older; dasiglucagon (stable liquid glucagon) has FDA approval for age 6 and older. The glucagon prefilled syringe/autoinjector is approved for ages ≥2 years. This relates to the age of children included in the trials that led to FDA approval. The clinician managing a child with T1D younger than age 4 or 6, has to decide whether to use standard glucagon or prescribe nasal glucagon or dasiglucagon off label.

Monitoring and evaluation

None.

Research priorities

Studies are needed on how often the new glucagon preparations are used, impact on resource utilization with use of newer glucagon preparations (e.g., EMS, hospitalization, etc. and evaluation of potential savings).

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