Special Report: Potential Strategies for Addressing GLP-1 and Dual GLP-1/GIP Receptor Agonist Shortages

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Unexpected drug shortages of the long-acting glucagon-like peptide 1 (GLP-1) receptor agonists dulaglutide and semaglutide and the dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist tirzepatide emerged in late 2022 and have persisted through the first quarter of 2023 (1). The drug shortage has not affected product doses equally; some doses are more widely available than others (2). For the purposes of this article, we will consider the dual GLP-1/GIP receptor agonist tirzepatide to be included when referring to GLP-1 receptor agonist product shortages. These shortages predominately occurred because of an unexpected increase in demand for GLP-1 receptor agonists without adequate adjustment in production (3). The inadequate supply has created new access barriers for patients previously using or wishing to initiate these products for glycemic management, weight loss, and/or cardiovascular risk reduction. Thus, strategies to mitigate this disruption to patient care are needed.

Disruptions in the supply chain create important challenges for patients and clinicians, forcing providers to seek alternative approaches to overcome what is hoped to be a temporary hurdle. Decreased availability and high cost have also led patients to seek alternative ways to obtain these medications. Many social media sites and online clinics claim to offer commercially available GLP-1 receptor agonist medications or even compounded versions at a discounted price. Although compounded medications are regulated and generally considered safe (4), compounded GLP-1 receptor agonists are unique. Each GLP-1 receptor agonist is only available as a branded medication manufactured by a single company. If the manufacturers are not supplying the compounding pharmacies with the active ingredient, then the source is unknown (5).

Past literature most commonly addresses drug shortages in the hospital setting and recommends a myriad of strategies, including stockpiling, using multiple or alternative suppliers, rationing among patients, substituting with alternative therapies, minimizing medication waste, maximizing utilization as long as possible based on manufacturer expiration date, adjusting formularies, and implementing formulary restrictions (6–9). Although few articles have outlined specific strategies to address this obstacle in the community/ambulatory setting, those available recommend contacting the supplier or another pharmacy, using other generic or brand-name options of the same medication, or switching to an alternative product altogether (10).

Given the lack of generic options within the GLP-1 receptor agonist class and the limited applicability of the other recommended approaches given the unique benefits of these therapies, this article sets out potential strategies that diabetes care teams can consider to overcome barriers related to the shortage. These suggestions are offered in the context of current persistent drug shortages and, while not ideal, are provided in the hope of mitigating undesired negative consequences from an inability of patients with type 2 diabetes to obtain GLP-1 receptor agonist therapies amid this global access challenge.

Considerations for Missed Doses and Alternative Dosing Strategies

Considerations for Missed Doses

Inconsistent use of drugs in the GLP-1 receptor agonist class is challenging because tolerance is developed to the common side effect of gastrointestinal (GI) disturbance with regular use. For this reason, most GLP-1 receptor agonists are initiated at the lowest available dose and titrated slowly, which helps to mitigate GI intolerance. However, it is not uncommon for patients to inadvertently miss doses (11). Manufacturers of GLP-1

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receptor agonists provide guidance on the resumption of therapy after a single missed dose, and this guidance varies by product and dosing interval (Table 1) (12–19). However, when a supply of a patient's GLP-1 receptor agonist is depleted and a refill is not available for an extended period, reinitiating at a lower dose to mitigate GI side effects once therapy can be resumed should be considered. Table 2 summarizes available recommendations and information to guide dose selection when resuming a GLP-1 receptor agonist after a more prolonged lapse in therapy (20,21).

Alternative Dosing Options

Until the shortage is resolved, alternative dosing strategies may temporarily help to maintain the desired weekly dose or extend the duration of a given supply. Potential strategies depend on the specific product's pen device.

Injectable Semaglutide

Semaglutide is available in an adjustable multidose pen that patients dial to a marked dose before injecting. This allows administration of alternative intermediate doses based on the number of "clicks" between each marked dose. Clinically, these intermediate doses are occasionally recommended to provide a more gradual dose titration to improve GI tolerability (22); however, this technique is not supported by the manufacturer (H.P.W., personal communication).

By applying this concept in reverse, a patient could potentially inject a lower dose using a more readily available higher-strength product, by dialing to an alternative number of clicks. If this strategy is used, special attention should be given to the product's shelf-life once opened, which is limited to 8 weeks (56 days) (Table 3) (13). Additionally, this method of using an intermediate dose may allow patients to extend the duration of a semaglutide pen and continue therapy, albeit with a lower-than-desired weekly dose. It is important to note that the pen concentration designed to deliver 0.25- and 0.5-mg doses recently changed from 2 mg/1.5 mL to 2 mg/3 mL (23). Furthermore, the concentrations of all semaglutide pens vary; consequently, the number of clicks to achieve a given dose also varies. For this reason, using clicks to administer alternative doses has a high potential for confusion and dosing

TABLE 1 Manufacturer Recommendations for Missed Doses of GLP-1 Receptor Agonists

Agent	Recommended Dosing Interval	Manufacturer Recommendations for Missed Doses
Short-acting agents		
Exenatide	Twice daily	• Skip missed dose and resume at the next scheduled dose.
Lixisenatide	Once daily	• If a dose is missed, administer within 1 hour prior to next meal.
Long-acting agents		
Dulaglutide	Once weekly	• Administer as soon as possible if there are ≥3 days (72 hours) until next scheduled dose. • If <3 days before next scheduled dose, skip the missed dose and administer on the next scheduled day.
Exenatide XR	Once weekly	• Administer as soon as possible if there are ≥3 days (72 hours) until the next scheduled dose. • If <3 days before next scheduled dose, skip the missed dose and administer on the next scheduled day.
Liraglutide	Once daily	• If dose is missed, resume with the next scheduled dose.
Semaglutide (injectable)	Once weekly	• Administer as soon as possible within 5 days after the missed dose. • If >5 days have passed, skip the dose and administer on the next scheduled day.
Semaglutide (oral)	Once daily	• If dose is missed, resume with the next scheduled dose.
Tirzepatide	Once weekly	• Administer as soon as possible within 4 days (96 hours) after the missed dose. • If >4 days have passed, skip the dose and administer on the next scheduled day.

TABLE 2 Considerations for Resuming a GLP-1 Receptor Agonist After a Prolonged Lapse in Therapy

Agent	Last Dose Administered	Recommendation(s) for Resuming Therapy
Dulaglutide*	1.5 mg once weekly	• Resume at 1.5 mg once-weekly dose. • Expect comparable tolerability to that experienced prior to dose interruption.
	3 or 4.5 mg once weekly	• Use best judgment if ≥3 doses are missed. ○ It is unknown whether tolerance to the GI adverse events will remain if reinitiated at the higher dose after ≥3 missed doses. ○ Decision can be informed by patient's prior GI tolerability. ○ In consideration of the above, clinicians may consider reinitiating at 1.5 mg once weekly.
Injectable semaglutide†	1 mg once weekly	• If ≤2 doses are missed, reinitiate at 1 mg once weekly. • If 3–4 doses are missed, reinitiate at 0.5 mg weekly. • If ≥5 doses are missed, reinitiate at 0.25 mg once weekly.
Tirzepatide‡	≥5 mg once weekly	• If ≤2 doses are missed, reinitiate at the same dose (provided the dose was adequately tolerated). • If ≥3 doses are missed, reinitiate at 5 mg once weekly.

*Based on manufacturer-provided information (20). †Based on personal communication with C. Wong on 27 February 2023. ‡Based on supplementary material published with ref. 21.

errors; however, it may be an option for continuing semaglutide therapy during the product shortage.

Dulaglutide and Tirzepatide

Unlike semaglutide, dulaglutide and tirzepatide are available only in single-use, single-dose pens. Although these agents are available in multiple strengths, each pen delivers a discrete and nonadjustable dose.

Currently, the 0.75- and 1.5-mg strengths of dulaglutide are more readily available than the 3- and 4.5-mg doses. Prescribing the 1.5-mg pen to be injected twice or thrice weekly as an equivalent to the 3- or 4.5-mg dosage, respectively, may be an alternative when higher-strength pens are unavailable. Although some sources recommend against this method because of potentially diminishing the supply of the lower doses (3), this dosing schedule was used in a phase 2 study (24) and thus can be considered a reasonable alternative (25).

A similar approach could be considered with tirzepatide, which is available in strengths of 2.5, 5, 7.5, 10, 12.5, and 15 mg (19). However, the manufacturer of tirzepatide recommends against the practice of additive multiple injections because it has not been studied (26). Outside of the increased burden to the patient of injecting multiple smaller doses to achieve the desired therapeutic dose, this practice may be reasonable when there are supply shortages of only higher-dose strengths, as presently experienced with dulaglutide.

Extended Interval Dosing

Although drug shortages may stimulate hospitals to ration medications among patients through an ethical allocation selection process (7), ambulatory patients may likewise choose to ration their own supply to lengthen the duration of their available GLP-1 receptor agonist product. To do so, patients may report

TABLE 3 Alternative Intermediate Doses of Injectable Semaglutide

Semaglutide Pen (Product Concentration)	Weekly Semaglutide Intermediate Doses					
0.25 and 0.5 mg (2 mg/3 mL)*	0.5 mg	0.4 mg	0.33 mg	0.25 mg	0.12 mg	0.06 mg
1 mg (4 mg/3 mL)	1 mg	0.8 mg	0.66 mg	0.5 mg	0.25 mg	0.12 mg
2 mg (8 mg/3 mL)	2 mg	1.6 mg	1.33 mg	1 mg	0.5 mg	0.25 mg
Number of clicks for desired intermediate dose	74	59	49	37	18	9
Number of available weekly doses using an intermediate dose	4	5	6	8	8†	8†

*New semaglutide pen concentration as of March 2023; doses not confirmed by the manufacturer but rather mathematically calculated by the authors. †Injected semaglutide is stable for 56 days (8 weeks) once opened and should be discarded thereafter.

intentionally extending the interval between doses and may inquire about how long they can safely delay their next dose without fully forfeiting efficacy. Because clinical trials and outcome studies are conducted with a specific dosing frequency in mind, the literature does not provide much of an evidence base to support extended dosing schedules. However, considerations for extending the dosing interval may be theorized according to the product's half-life. It is important to note that these adjustments are theoretical and may not translate into a clinically supported outcome; however, in times of supply shortages, it may be preferred to a cessation of therapy for an extended period.

Interchanging GLP-1 Receptor Agonist Therapies

Selecting a Therapeutic Equivalent Dose for Glucose Lowering

Although there are other reasons for interchanging one GLP-1 receptor agonist for another agent in the class (e.g., enhanced glucose efficacy, better weight loss, improved tolerability, and cost), the present rationale is to sidestep limited access caused by the drug shortage. In time, results from several studies will guide equivalent dosing interchanges within the GLP-1 receptor agonist class (27,28). Several head-to-head studies have been conducted comparing one GLP-1 receptor agonist to another, but no study exists comparing doses among all of the agents in this class. Thus, establishing dosing equivalence is challenging but can be valuable in a real-world clinical setting (29,30).

Indirect comparisons among studies provide insight to developing this practical guidance. Trujillo et al. (31,32) provided comprehensive analyses of GLP-1 receptor agonist investigations using active comparative treatment arms. Since these analyses were published, higher GLP-1 receptor agonist therapeutic doses have gained U.S. Food and Drug Administration (FDA) approval, and new products such as the dual GLP-1/GIP receptor agonist tirzepatide have reached the market; these newer products must also be considered in the spectrum of dosing equivalents within the therapeutic class (19,33,34). Table 4 offers a suggested comparison of the equivalent doses for currently available GLP-1 receptor agonists based on their glycemic impact (31–35). This information can support clinical decision-making, especially during this time of GLP-1 receptor agonist shortages.

Methods for Interchanging GLP-1 Receptor Agonists

The nidus prompting the therapeutic interchange guides the method by which a GLP-1 receptor agonist substitution should occur. If the interchange is desired to overcome a supply shortage, initiating the new agent in place of the original product at an equivalent dose is reasonable (Table 4) (29,30). However, an equivalent dose chart should be used as a starting guide. Additional patient-specific factors to consider include the current degree of glucose control and potential need for additional glucose lowering, the length of time the patient has been off the medication, and how the patient tolerated the GLP-1 receptor agonist initially. When switching from a product administered once or twice

TABLE 4 GLP-1 Receptor Agonist Drug Shortages and Suggested Comparative Doses for Treating Type 2 Diabetes

Agent	Dosing Route and Interval	Comparative Doses								
Exenatide	SC twice daily	5 μg*	10 μg							
Lixisenatide	SC once daily	10 μg*	20 μg							
Liraglutide	SC once daily	0.6 mg*	1.2 mg	1.8 mg						
Exenatide XR	SC once weekly			2 mg						
Dulaglutide	SC once weekly		0.75 mg[a]*	1.5 mg[a]	3 mg[b]†	4.5 mg[b]†				
Semaglutide	SC once weekly		0.25 mg[b]*	0.5 mg[b]		1 mg[a]	2 mg[a]‡			
Semaglutide	PO once daily	3 mg*	7 mg	14 mg						
Tirzepatide	SC once weekly			2.5 mg[a]*			5 mg[a]‡	7.5 mg[a]	10 mg[a]	12.5 mg[a]	15 mg[a]

According to the FDA's drug shortage database as of 10 March 2023 (2), patients may have limited or intermittent access in community pharmacies to three agents in varying doses: dulaglutide, injectable semaglutide, and tirzepatide. [a]Drug doses that are currently in short supply but still available. [b]Drug doses with only limited or intermittent availability. *Comparative efficacy of starting doses is not known and based on the clinical judgement of authors. †Based on information from ref. 33. ‡Based on information from ref. 35. PO, by mouth; SC, subcutaneous.

daily, begin use of the new product the day after discontinuing the original product. When switching from a weekly administered product, begin the new product 7 days after discontinuing the original product.

Managing Prior Authorizations

Interchanging a GLP-1 receptor agonist in short supply with an available one may require prescribing a nonformulary product or one that requires prior authorization. Maintaining a collaborative line of communication between the prescriber and the pharmacy may help to facilitate access to the alternative GLP-1 receptor agonist (36). Open communication may also help prescribers identify available GLP-1 receptor agonists and likewise may prompt community pharmacists to efficiently return prior authorization requests to prescribers. Clear documentation in the medical record explaining the reason, importance, and necessity of the GLP-1 receptor agonist interchange also may expedite access for patients. Designating a staff member to complete prior authorizations will additionally facilitate the process (7). Lastly, it would be reasonable for managed care organizations to provide leniency for the use of alternative GLP-1 receptor agonist therapies when a preferred agent is in short supply.

Avoiding New GLP-1 Receptor Agonist Prescriptions and Using Alternative Antihyperglycemic Agents

During drug shortages, when possible, avoid prescribing medications that are in short supply for a drug-naive patient (3). If comparable GLP-1 receptor agonists are also unavailable, considering the use of another antihyperglycemic treatment may be necessary to control a patient's glycemic status instead of prescribing a new GLP-1 receptor agonist (9). The alternative therapy should be selected through shared decision-making to identify the most appropriate product based on a given patient's needs and preferences. Once the GLP-1 receptor agonist shortage resolves, the preferred therapy can be added or interchanged with the temporary agent.

For patients with chronic kidney disease, heart failure, or established atherosclerotic cardiovascular disease (ASCVD) or those at high risk for ASCVD, substituting a sodium–glucose cotransporter 2 (SGLT2) inhibitor may be a preferred choice (37). Products from this class are taken by mouth once daily, have a negligible risk of causing hypoglycemia, and also facilitate weight loss. Additionally, like several of the GLP-1 receptor agonists, SGLT2 inhibitors have benefits that extend beyond glucose control. Many hold extended FDA indications for reducing the risk of major adverse cardiovascular events, cardiovascular death, and/or hospitalization for heart failure or for slowing decline in kidney function. Although not as robust at lowering glucose or weight as some of the long-acting GLP-1 receptor agonists, SGLT2 inhibitors are a reasonable substitute, particularly for patients with type 2 diabetes and compelling conditions.

Because of the overlapping mechanisms of dipeptidyl peptidase 4 (DPP-4) inhibitors, a product from this class may be a reasonable selection for temporary use in place of a GLP-1 receptor agonist. Similar to short-acting GLP-1 receptor agonists, DPP-4 inhibitors provide postprandial glucose reduction with a minimal impact on fasting blood glucose; yet, their A1C benefit is considerably less, particularly when compared with the glycemic efficacy of long-acting GLP-1 receptor agonists. Substituting a DPP-4 inhibitor for a long-acting GLP-1 receptor agonist will leave the patient's fasting blood glucose component unaddressed and may therefore require the addition of another agent. However, the DPP-4 inhibitors are conveniently dosed by mouth once daily without regard to meals.

Other options are also available as an alternative to GLP-1 receptor agonists if not already in use, including metformin, thiazolidinediones (TZDs), sulfonylureas, or basal insulin. As with any other therapy, risks, benefits, cost, dosing frequency, and method of administration should be considered with the patient to bridge the unavailability of the preferred therapy. It is worthwhile to reevaluate metformin therapy if the patient is not using metformin or the dose is not maximized. Metformin effectively lowers glucose without the risk of hypoglycemia or weight gain. TZDs are another option that offers good glycemic control and a low risk of hypoglycemia, but they are limited by side effects, including weight gain and edema. Sulfonylureas effectively lower A1C but increase the risk of hypoglycemia and facilitate weight gain. Still, these agents are all low-cost and easily administered once or twice daily by mouth. Basal insulin is another option to lower glucose. The dose can be individualized based on blood glucose monitoring. However, like sulfonylureas, basal insulin also increases the risk of hypoglycemia and weight gain.

Patient Education Through the GLP-1 Receptor Agonist Shortage

Regardless of the method selected to overcome the current limited access to GLP-1 receptor agonists, educating

patients and setting expectations during the transitional period is time well spent. Caution patients to consider the credibility and reliability of online sources and explain the concerns related to compounded products (4,5).

For interchanged GLP-1 receptor agonists, provide adequate education about the new delivery device or method of administration, given that administration routes, dosing frequencies, and delivery devices are not universal among GLP-1 receptor agonists; the nuances for administration are not intuitive to patients. Using a demonstration device at the time of prescribing and dispensing can help overcome administration challenges at home.

For alternative pharmacotherapies, help to set expectations regarding side effect profiles, onset of benefit, and dosing schedules. Finally, it is prudent to advise patients to self-monitor their blood glucose more frequently during therapy transition to identify and mitigate hyperglycemia and hypoglycemia (38). Review glycemic goals and discuss an action plan for managing glucose excursions to avoid the need for urgent or emergent care.

Conclusions

Drug shortages are inconvenient to patients, providers, and the health care system, and the GLP-1 receptor agonist shortage has been no exception. Adequate adjustments to patients' medications are necessary to sidestep the risk of hyperglycemia resulting from the unavailability of preferred GLP-1 receptor agonist drugs. Several options are available, although not necessarily ideal. Once the drug shortage is resolved, patients, in collaboration with their providers, may choose to reinitiate their preferred GLP-1 receptor agonist therapy to optimize their diabetes management.

DUALITY OF INTEREST

H.P.W. is an advisor for Abbott Laboratories. J.M.T. is an advisor to Novo Nordisk and Sanofi. J.J.N. is a speaker for Dexcom, a consultant to Bayer, and an advisor to Boehringer Ingelheim, Eli Lilly, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

H.P.W. researched data and wrote the manuscript. J.M.T. and J.J.N. researched data and reviewed/edited the manuscript. H.P.W. is the guarantor of this work and, as such, had full access to all the information reported and takes responsibility for the integrity of the content.

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