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ISMP
An ECRI Affiliate

Community/Ambulatory Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

Communication issues and dosing errors possible with GLP-1 microdosing

Problem: Over the past few years, interest in the use of glucagon-like peptide-1 (GLP-1) receptor agonists to help patients manage their weight and diabetes has exploded. GLP-1 receptor agonists (e.g., **OZEMPIC** [semaglutide], **VICTOZA** [liraglutide], **MOUNJARO** [tirzepatide]) were originally developed and approved to treat patients with type 2 diabetes by improving glycemic control, along with diet and exercise. More recently, GLP-1 receptor agonists (e.g., **WEGOVY** [semaglutide], **SAXENDA** [liraglutide], **ZEPBOUND** [tirzepatide]) have been approved for chronic weight management.

As we discussed in our February 2024 article, *Increased demand and shortages of GLP-1 receptor agonists contributes to patient harm*, all this interest led to a dramatic increase in demand for the products and resulted in long-lasting drug shortages for many of them. As a result, providers and patients sought alternate sources for these medications, including compounding pharmacies, weight-loss clinics, and others. Unfortunately, ISMP, the US Food and Drug Administration (FDA), and America's Poison Centers have received reports of errors and adverse events following patient use of compounded GLP-1 receptor agonists.

Most of the GLP-1 receptor agonists are injectable products available in prefilled pen devices (**Table 1**). Recently we learned from a specialty pharmacy that, for a variety of reasons, some providers and patients using GLP-1 receptor agonists for weight management are manipulating the pens to administer intermediate doses using a technique referred to as microdosing or click counting.

Table 1. Prefilled pen configuration for available injectable GLP-1 receptor agonists.

Medication	Indication	Type of prefilled pen
Ozempic (semaglutide)	Diabetes, Type 2	Multi-use pen, dial the dose
Wegovy (semaglutide)	Weight management	Single-use pen, no dose dialing
Victoza (liraglutide)	Diabetes, Type 2	Multi-use pen, dial the dose
Saxenda (liraglutide)	Weight management	Multi-use pen, dial the dose
Mounjaro (tirzepatide)	Diabetes, Type 2	Single-use pen, no dose dialing
Zepbound (tirzepatide)	Weight management	Single-use pen, no dose dialing

GLP-1 receptor agonist microdosing

Microdosing (or click counting) involves purposefully injecting less medication than the FDA-approved or typical prescribed dose. Providers and patients may microdose for several reasons, including reducing mild but undesirable side effects, maintaining desired weight loss with a lower dose, reducing treatment costs, and extending the use of a single pen device when the medication is difficult to obtain. One specialty pharmacy shared a dosing table their providers are using to prescribe a microdose along with the corresponding number of clicks (**Figure 1**, page 2). Currently, three products, Ozempic, Saxenda, and Victoza, are available in dose-adjustable prefilled pens that can accommodate microdosing. The pen devices for Wegovy, Mounjaro, and Zepbound come in fixed-dose, single-use pens and thus cannot be used for microdosing. The dose-adjustable pens

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Safety considerations during fluid shortages

Problem: On September 29, 2024, Baxter announced that their North Cove, NC, manufacturing plant was temporarily closed due to damage from Hurricane Helene. This facility is the production site for several intravenous (IV), parenteral nutrition (PN), peritoneal dialysis (PD), and cardioplegic fluids/solutions. While Baxter has resumed production of some fluids at this site, the delay has resulted in the need for Baxter to invoke product allocations to healthcare organizations. ISMP has been in communication with Baxter, the US Food and Drug Administration (FDA), the American Society of Health-System Pharmacists (ASHP), and several other organizations to advocate for safe fluid conservation practices. ASHP and the University of Utah are providing ongoing updates to their *Small- and Large-Volume Fluid Shortages – Suggestions for Management and Conservation* resource. In addition, the FDA announced it is working with Baxter to temporarily import some products to help meet patient needs. Baxter has established a webpage with resources and additional information for imported products and those with extended expiration dates.

Any change to procedures, workflows, or products because of the shortage may increase the risk of error. The following represent examples of safety concerns and unsafe practices that must be addressed and avoided.

- ☐ Using source bags or bottles as diluents for multiple patients. For example, some practitioners may feel it is necessary to manipulate fluid bags to prepare smaller aliquots from the bag into syringes. When this is done outside of a pharmacy's sterile compounding area and without IV workflow management systems (IVWMS), the risk of contamination and error is high. This practice has contributed to disease outbreaks in the past.

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have dose markings for each FDA-approved dose. As patients advance from one dose to the next, the pen dial clicks. To dial a microdose, patients are advised to count the clicks made when turning the pen device's dosing knob instead of dialing the knob to the dose number.

Following the report we received, our colleagues at ECRI conducted a curated literature search looking for evidence supporting the safety and efficacy of microdosing.[1] They found no studies reporting on GLP-1 receptor agonist microdose regimens. They also identified no clinical or bench studies on the accuracy and safety of delivering microdoses using Ozempic, Saxenda, or Victoza pens. While no studies provide evidence to support microdosing, ECRI previously reviewed a large body of clinical evidence that shows GLP-1 receptor agonists are safe and effective even at submaximal doses within the recommended dose ranges listed in the medication labeling.[2]

Number of Ozempic (Semaglutide) Pen Clicks

Desired dose	0.25 or 0.5 mg (2 mg/3 mL)	1 mg (4 mg/3 mL)	2 mg (8 mg/3 mL)
0.125 mg	18	9	4
0.25 mg	36	18	9
0.5 mg	72	36	18
0.75 mg	-	54	27
1.0 mg	-	72	36
1.25 mg	-	-	45
1.5 mg	-	-	54
1.75 mg	-	-	63
2.0 mg	-	-	72

Figure 1. An example of a dosing table providers use to determine the number of clicks for a given Ozempic (semaglutide) microdose.

It should be noted that Novo Nordisk, the manufacturer of liraglutide and semaglutide, recommends against using the click-counting method for delivering GLP-1 receptor agonist doses. However, media stories and other sources confirm that some physicians are recommending microdosing by click counting.[1] We also found a large number of podcasts available on the subject. So, it appears that microdosing may be a pervasive practice.

Identified safety concerns

Following ISMP and ECRI's internal discussion as well as those with various specialty pharmacies, we have identified a number of safety concerns with microdosing, including the following:

- According to information from specialty pharmacies, despite directing patients to use click counting for an unlabeled dose, providers are writing prescriptions for these products using FDA-approved doses (e.g., 0.25 mg, 0.5 mg, 1 mg, 2 mg for semaglutide). As a result, prescription directions provided to the pharmacy and printed on the prescription label do not match the information the prescriber has provided to the patient. This could lead pharmacists to educate patients on the wrong dose and can contribute to subsequent dosing errors.
- Since prescriptions for these drugs are being written for approved dosing, if the patient is microdosing at home, the prescription and dispensing history will not match. This can result in wrong dose errors during transitions of care and when patients are admitted to hospitals. For example, the dispensing history may show the patient received an Ozempic 2 mg pen with directions to inject 2 mg weekly. However, the patient may be counting clicks to only administer a 0.75 mg weekly dose. If the patient-specific dosing is not collected in addition to the dispensing history, the inpatient provider may order the higher dose leading to adverse effects for the patient.
- Dialing and counting to the correct number of clicks may be difficult for some patients with dexterity or auditory issues. Also, when counting a high number of clicks (e.g., 36, 54), a patient may easily be distracted and miscount. In either scenario, the wrong dose may be administered.
- Pharmacies may be unaware of the actual number of pen needles a patient needs should the prescription contain FDA-approved dosing but the patient has been given alternative instructions. As a result, patients may not have enough pen needles to last beyond the expected days' supply and may be tempted to reuse pen needles.

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- ☐ New products purchased from an alternative manufacturer or imported (which may present unforeseen labeling and nomenclature issues) may contribute to mix-ups due to look-alike product packaging/labeling.
- ☐ FDA has temporarily approved the importation of glucose injection (anhydrous form of glucose), that is not directly interchangeable from a concentration standpoint with FDA-approved dextrose injection, USP (hydrated form of glucose). Also, the caloric content of these products are different.
- ☐ Concentrated 23.4% sodium chloride injection may be obtained and used to compound solutions of 0.9% sodium chloride for injection outside of pharmacy.
- ☐ Missing or unscannable barcodes (e.g., imported products) may lead to practitioners bypassing barcode medication administration (BCMA).
- ☐ An expired product may be administered due to confusion about the product's extended expiration date.

Safe Practice Recommendations: When implementing fluid conservation strategies, consider the following recommendations.

Evaluate systems. Evaluate all systems impacted by workflow or product changes due to the shortage. Review order sets and treatment protocols and make changes based on available products (and likewise when shortages end). Consider changes in the electronic health record (EHR) to allow the use of either dextrose or saline for the admixture of drugs compatible with both solutions (considering any critical carbohydrate or sodium restrictions that the patient may have). Use EHR alerts or forcing functions when a drug is compatible with only one diluent. Update smart infusion pump drug libraries.

Evaluate FDA-approved imported products. Carefully review the information in the letter accompanying imported products, which can be found here: Baxter Resources for Products Authorized for Temporary Importation. As an example, organizations must consider any differences between glucose and

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- After administering the first dose, the Ozempic pen device should be discarded after 56 days. However, in cases where a larger pen size is prescribed for a low microdose, there is the risk that patients may use the pen for more than 56 days.

Safe Practice Recommendations: While ISMP is not in a position to endorse the use of microdosing for GLP-1 receptor agonists, it appears this practice may be more widespread than originally thought. Consider the following recommendations to prevent dose-related errors with microdosing of GLP-1 receptor agonists:

Providers

- Before prescribing microdosing regimens, assess the patient's ability to count the prescribed number of clicks accurately and consistently.
- Provide patients with clear verbal and written instructions for their microdose regimen.
- Fully document the patient's microdose and the prescribed number of clicks in the medical record.
- Share the prescribed microdose and number of clicks with the dispensing pharmacy to enable them to support the patient's accurate dose measurement.

Pharmacists

- Provide patient counseling when dispensing GLP-1 receptor agonists.
- Verify with the patient their current stage of the dose escalation schedule.
- Ask the patient the dose that they are taking or have been directed to take by their prescriber.
- Advise the patient about the potential adverse effects of the drugs and when to follow up with their provider for intervention.
- Share this information with staff so that they are aware that providers may prescribe microdoses of GLP-1 receptor agonists and prescription directions may differ.

Transitions of care

- Obtain the most accurate medication list feasible. In a hospital or residential care setting, obtain this list before the first dose of medication is administered (except in emergency or urgent situations).
- Do not assume the documented dose is the current dose the patient is taking. Add scripting to your medication reconciliation procedures that specifically asks patients about their actual dose of a GLP-1 receptor agonist. If the patient is unable to answer the question, confirm the patient's dose with their provider or caregiver.

Patients and families

- Educate patients to maintain (and share) an up-to-date list of their medications, including the doses they are actually taking.
- Encourage patients and family members to ask questions about the prescribed drug and dose, including when the dose communicated by the prescriber is different than what is printed on the prescription label. Also, support patients and family members to speak up about any concerns about the patient's ability to count the required number of clicks.

References

1. ECRI. Clinical evidence assessment: GLP-1 microdosing in patients with obesity curated literature search. October 2024. Accessed November 11, 2024.
2. ECRI. Clinical evidence assessment: Best clinical practices for managing obesity and overweight with GLP-1 receptor agonists. January 2024. Accessed November 11, 2024.

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dextrose products (e.g., caloric content, pH, osmolarity) and update protocols and systems (e.g., EHR, automated compounding device [ACD]). The Baxter Resources for Products Authorized for Temporary Importation page includes educational material on how to add concentrated glucose (as glucose 50% or as the equivalent of dextrose 55%) to the Baxter order entry software (Abacus) and ACD (ExactaMix). Additional information on the differences between glucose and dextrose can be found in Webinars & Videos which address compatibility, concentration, and energy content. Also, ISMP has created an ***Imported Fluid Product Checklist*** for organizations to use when evaluating any imported products' safety during the current fluid shortage.

Conduct a proactive safety analysis. When a new product is procured (i.e., from an alternative manufacturer or imported), conduct a review to identify potential risks with the product's design, including look-alike labeling and packaging concerns with other products in use within the organization. Store look-alike products separately, and consider the use of signage in storage locations, or other warnings such as auxiliary labels. Do not store 1,000 mL bags of sterile water for injection, irrigation, or inhalation in patient care areas. Test all product barcodes prior to distribution to identify and mitigate any issues.

Follow proper infection prevention practices. Never use bags of solutions as a common source of supply for more than one patient and never administer medications from the same syringe to more than one patient.

Safeguard IV push practices. If switching from an infusion to IV push when the patient's clinical status and drug properties (e.g., pH, osmolarity) allow, follow the recommendations listed in the ***ISMP Safe Practice Guidelines for Adult IV Push Medications***. Pharmacy should prepare and dispense medications that may be administered IV push in ready-to-administer concentrations in appropriate syringes. The syringe of diluted medication should be labeled with the patient's name, drug name, strength, dose, rate of administration (e.g., slow IV push over 5 minutes), and the beyond-use date/time.

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Use of electronic prescription prescriber note field contributes to error

Over the years, ISMP has received numerous error reports when the field for "Comments" or "Prescriber Note" on electronic prescriptions (e-prescriptions) is used to express a different set of directions than what is included in the *sig* field or to clarify the medication order. In a recent event, a specialty pharmacy reported that a provider ordered **DEPAKOTE ER** (divalproex sodium) 500 mg extended-release tablets for a patient. In the *sig* field, the directions read, "Take 5 Tablet By Mouth As Directed - See Instructions"(**Figure 1**). The prescriber also included more detailed instructions in the "Prescribers Note" field at the bottom of the e-prescription which stated, "Take 1 tab by mouth every morning and 1 tab every evening and 3 tabs at bedtime." Because the more specific instructions were included in the notes field and not the *sig* field, the pharmacy computer system did not autopopulate them, requiring manual entry. During the transcription process, the data entry technician missed part of the directions. The verification pharmacist did not catch the transcription error, and the prescription was dispensed with incorrect directions. The error was discovered at the first refill when the pharmacist double-checked the prescription directions against the original prescription. Thankfully, the patient was taking the medication correctly as they had been on this regimen for quite some time.

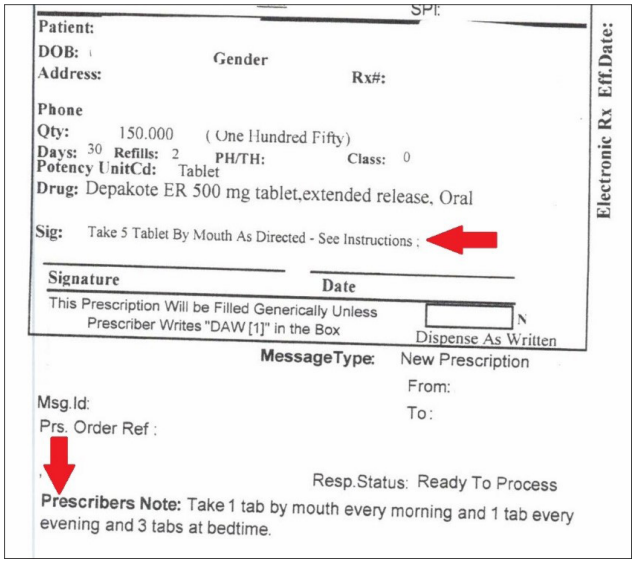


Figure 1. A prescriber included instructions in the e-prescription's *sig* field (horizontal red arrow) and a more specific set of instructions in the Prescribers Note field (downward pointing red arrow).

We have received similar reports from community pharmacists. For example, a community pharmacy received an e-prescription for the anticonvulsant gabapentin with "1 tablet PO TID" in the *sig* field but "i po bid x7 days, then i po tid thereafter" in the notes field.

Using the comment or notes field to correct or modify electronic orders is problematic as pharmacy staff may miss the information. Or, as in the case above, mistakes may be made when manually transcribing the information during data entry. Organizations should establish an escalation strategy for when staff and prescribers cannot enter the correct information (e.g., dose, frequency) into the electronic prescribing system. If two sets of directions are seen on an e-prescription (i.e., in the *sig* and in the notes), pharmacy staff should seek clarification from the prescriber prior to dispensing. Pharmacists should inform and educate prescribers when potential or actual errors are encountered as a result of using the comments or prescriber notes field.

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Monitor expiration dates. Baxter is now authorized by FDA to extend the use dates of some products to provide a 24-month expiration from the date of manufacture (Hurricane Helene Clinical Resources for US Healthcare Professionals, scroll to Expiration Dating Extension to 24 Months). Review this information to determine if a product has an extended expiration date, and if so, implement a process (e.g., make staff aware and update the expiration date on the label) to ensure staff know when the product will expire.

Maximize the use of IVWMS. Use IVWMS in the pharmacy when manipulating or compounding all products. IVWMS should also be used when aliquoting from large containers to smaller "unit-dose" containers (i.e., large-volume parenteral to a syringe).

Educate practitioners. Communicate changes to policies and practices, systems, and when new products are purchased, so staff are aware of any potential safety concerns. Provide competency assessments related to impacted technologies, including a broad spectrum of scenarios (e.g., incorrect drug alert upon scanning) that staff might encounter. If a medication is lacking a scannable barcode, the practitioner must confirm the product's identity prior to administration. Develop an escalation and reporting process when a medication barcode will not scan. Gather staff feedback about safety concerns related to shortages during huddles.

Report errors and share lessons learned. Report medication errors, close calls, and hazards to ISMP.

Additional Resources.

1) ECRI: *Patient safety nonprofit releases guidance for navigating medical supply chain disruptions caused by Hurricane Helene*
2) Baxter: *Hurricane Helene Updates*
3) American Society for Parenteral and Enteral Nutrition (ASPEN): Shortage recommendations for intravenous dextrose and sterile water for injection
4) End Drug Shortages Alliance: *Resources*

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Tuesday, December 10, 2024

Civic Theatre – New Orleans 6:00 pm

2024 Michael R. Cohen Lifetime Achievement Award Winner



David W. Bates, MD, MSc

David W. Bates, MD, MSc, Medical Director of Clinical and Quality Analysis, Mass General Brigham; Senior Physician and Director, Center for Patient Safety Research and Practice, Brigham and Women's Hospital; Professor, Harvard Medical School and Harvard T.H. Chan School of Public Health

Join us in December for our annual Cheers Awards celebration, where we will celebrate the amazing abilities of individuals and organizations that have advanced medication safety in the past year.

You can help share their **"magic"** with the healthcare community by attending the awards dinner and/or supporting the event! Your participation brings attention to advances in medication safety and enables ISMP to continue its lifesaving work.

For support opportunities and/or to register for the dinner, visit: www.ismp.org/cheers

Educational Sessions with ISMP Speakers at the 2024 ASHP Midyear Clinical Meeting

Please stop by and see us in booth #1813!

Tuesday, December 10, 2024

ISMP Medication Safety Update 2024
8:00 am – 9:30 am CT
Room 272 Level 2

Get in Top Form with the 2024 Health Technology and Patient Safety Hazards
2:00 pm – 3:00 pm CT
Room 272 Level 2

The (Not So) Big Easy of Safety: Measuring Meaningfully
3:30 pm – 4:45 pm CT
Room TBD

Wednesday, December 11, 2024

Executive View: Leaders Discuss Drug Shortage Policy and IV Fluid Updates
7:45 am – 9:45 am CT
Room TBD

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