Injectable glucagon-like peptide-1 (GLP-1) receptor agonists and oral dipeptidyl peptidase-4 (DPP-4) inhibitors are incretin-based therapies that offer a unique approach to effective and durable glycemic control in type 2 diabetes. Like all medications, they also have some predictable adverse effects. Pharmacists who take time to educate patients and prescribers about ways to minimize and manage adverse effects can help to ensure optimal treatment outcomes.

**Nausea**
Transient, dose-related nausea is the most common adverse effect of therapy with GLP-1 receptor agonists. When nausea occurred during clinical trials, it generally was mild to moderate in severity, peaked during the initial weeks of therapy, and subsided with continued use.

The key strategy for attenuating nausea is to initiate GLP-1 receptor agonist therapy at a low dose. Following the recommended dose titration schedules (see Table) helps to reduce both the likelihood and severity of nausea. It is important to note that the initial dosage of liraglutide (0.6 mg daily) does not provide durable glycemic control in type 2 diabetes.

Anecdotal approaches to preventing or reducing nausea during exenatide therapy include:

- Initiating therapy at a dosage of 5 µg once daily (rather than twice daily).
- Reducing the initial dosage from 5 µg twice daily to 5 µg once daily for several weeks.
- Maintaining the lower dosage of 5 µg twice daily for longer than 4 weeks.

In some patients, the occurrence of nausea is more accurately described as a bloated feeling or a sense of gastric fullness after eating, most likely related to delayed gastric emptying. There appears to be an association between nausea during GLP-1 receptor agonist therapy and both the fat content and size of meals; accordingly, limiting or avoiding fatty or fried foods and eating smaller portions at mealtimes may help to prevent the feeling of nausea.

Patients may obtain some relief from nausea by consuming ginger (e.g., fresh ginger, ginger tea), soda crackers, or rice crackers. Slowly sipping hot water or sucking on sugar-free mints also may ease nausea. Pharmacologic options may help to prevent the feeling of nausea.

**The Table**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exenatide</strong></td>
<td>Initial Dosage: 5 µg twice daily</td>
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<tr>
<td></td>
<td>Optional Dose Escalation: 10 µg twice daily</td>
</tr>
<tr>
<td><strong>Liraglutide</strong></td>
<td>0.6 mg once daily for 1 week, then increase to 1.2 mg once daily</td>
</tr>
</tbody>
</table>

- *For all patients.
- *As needed for acceptable glycemic control.

GLP-1 = glucagon-like peptide-1.

**Hypoglycemia**
The risk of mild to moderate hypoglycemia with incretin-based agents is increased in two specific situations:

- When GLP-1 receptor agonists or DPP-4 inhibitors are used in conjunction with a sulfonylurea (or possibly other insulin secretagogues, such as meglitinides).
- If a patient injects a dose of exenatide but is unable to eat for more than 1 hour after the injection.

In the first instance, consideration should be given to reducing the dose of the sulfonylurea or secretagogue. In the exenatide scenario, patients should know to watch for symptoms of hypoglycemia if a meal is delayed, as well as to avoid driving or performing other dangerous tasks until after they have eaten something. Conversely, patients who eat and then realize that they neglected to administer a dose of exenatide should be advised to skip that dose and resume treatment with the next scheduled dose. Patients should not inject an extra dose or increase the amount of a subsequent dose; doing so increases the risk of gastrointestinal adverse effects.

**Hypersensitivity Reactions**
Some patients have experienced hypersensitivity reactions during treatment with GLP-1 receptor agonists or DPP-4 inhibitors. Although many of these reactions have been relatively mild (e.g., urticaria, facial edema), patients also have experienced serious reactions such as anaphylaxis, angioedema, and (with sitagliptin) exfoliative skin conditions including Stevens-Johnson syndrome. Some cases have occurred after the first dose.

Pharmacists should ensure that patients can recognize symptoms of a possible hypersensitivity reaction. Patients should be advised to stop using the medication and seek medical attention or emergency care if these symptoms occur. Treatment should not be resumed if a hypersensitivity reaction is suspected.
Managing Adverse Effects of GLP-1 Receptor Agonists and DPP-4 Inhibitors

Instructions: The assessment questions printed below allow you to preview the online CPE exam. Please review all of your answers to be sure you have marked the proper letter on the online CPE exam. There is only one correct answer to each question.

1. Which of the following adverse effects is identified in this activity as a possible consequence of therapy with either glucagon-like peptide-1 (GLP-1) receptor agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors?
   a. Headache.
   b. Hypersensitivity reactions.
   c. Nausea.
   d. Urinary tract infection.

2. The key strategy for minimizing nausea associated with GLP-1 receptor agonist therapy is to:
   a. Administer doses immediately after meals.
   b. Consume smaller portions at mealtimes.
   c. Initiate treatment at a low dose and titrate as recommended and tolerated.
   d. Sip hot water slowly for 15 minutes before administering each dose.

3. The risk of hypoglycemia is increased when incretin-based agents are used as combination therapy with:
   a. Metformin.
   b. Pramlintide.
   c. Sulfonylureas.
   d. Thiazolidinediones.

CPE Instructions

Completing a posttest at www.pharmacist.com/education is as easy as 1-2-3…

1. Go to Online CPE Quick List and click on the title of this activity.
2. Log in. APhA members enter your user name and password. Not an APhA member? Just click “Create one now” to open an account. No fee is required to register.
3. Successfully complete the CPE exam and evaluation form to gain immediate access to your Statement of Credit.

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