Diabetes mellitus (DM) is a metabolic disorder that results in high blood sugars, that if left untreated, may lead to chronic complications including blindness, kidney disease, extremity amputation, cardiovascular disease, and neuropathy. In 2010, it was estimated that 26 million Americans 20 years and older have DM, with a fourth of these patients not knowing. An additional 79 million Americans are at high risk of developing this progressive disease. Type 2 diabetes mellitus (T2DM) accounts for 90% of all DM cases, and is characterized by resistance to the action of insulin, insufficient insulin secretion, or both. 

Current diabetes guidelines recommend lifestyle changes first, and then pharmacologic therapy with metformin if the A1c goal is not reached after three months. Dual therapy can be considered after a three month trial and failure of metformin. The guidelines do not recommend a specific second agent, which allows the clinician to choose between a sulfonylurea, thiazolidinedione (TZD), dipeptidyl peptidase-4 inhibitor (DPP-4), sugar glucose transporter-2 inhibitor (SGLT2), glucagon-like peptide agonist (GLP-1), or insulin based on patient factors. The GLP-1 agonists Victoza (liraglutide), Byetta and Bydureon (exenatide), Tanzeum (albiglutide), and Trulicity (dulaglutide) will be discussed in this article.

GLP-1 is a peptide hormone that increases insulin release from the pancreas in a glucose-dependent manner, while decreasing the glucagon secretion. The result is decreased blood glucose, weight loss, delayed gastric emptying, and increased satiety. All medications in this class are administered through subcutaneous injection. The average expected A1c reduction for the class is 1-1.5%. Weight loss of 1-2.5 kg can be expected. Properties of each medication vary throughout the class as seen in the chart on page 3 (adapted from Pharmacist’s Letter). Dosing and administration instructions vary between agents. Twice daily exenatide and liraglutide are dosed the most frequently, with newer agents being dosed. All medications can be taken without regards to meals, except twice daily exenatide, which must be injected 60 minutes before the morning and evening meal. Weekly exenatide and albiglutide require reconstitution before injecting, while the other ones do not; patient training to properly reconstitute these medications is recommended. Both exenatide formulations should be avoided if CrCl is less than 30 ml/min. No adjustments for renal dysfunction are available for the other medications.

The side effect profile of GLP-1 agonists is fairly mild with discontinuation rates of less than 10% for any adverse effect. Nausea, vomiting, diarrhea, constipation, and injection site reactions are the most common adverse effects. Long-acting agents seem to have less nausea and vomiting compared to shorter acting agents, most likely due to decreased plasma
fluctuations. Injection site reactions are increased with the agents that are dosed weekly and patients may develop nodules under the skin. Upper respiratory tract infections (URI) have also been noted across all trials for each of the medications (4-11%). The mechanism for increased risk is still undetermined. The risk of hypoglycemia is low due to the glucose dependent mechanism. Major hypoglycemia occurs in less than 1% of patients when GLP-1 agonists are not used in combination with sulfonylureas. However, hypoglycemia symptoms should still be monitored, especially if GLP-1 agonists are taken concurrently with other anti-diabetic medications.5

Precautions with GLP-1 agonists include pancreatitis and C-cell thyroid tumors.6 Patients with T2DM are already two to three times more likely to get pancreatitis; it is still undetermined if the risk for pancreatitis is associated with the medications, or the natural changes of the pancreas in T2DM patients. C-cell tumors have been identified in animal studies, but have yet to be found in humans. It is still recommended to avoid use in patients with a history of pancreatitis or thyroid cancer.6 Data is expected in 2015-2019 regarding cardiac outcomes with this class of medications. Preliminary data has shown a decrease in blood pressure, but an increase in heart rate with the once weekly formulations.6

GLP-1 agonists do not have many direct drug interactions. Due to decreased gastric motility, the absorption of medications may be altered.4 Post-marketing studies have reported an increase in INR while using GLP-1 agonists.3,4 INR levels should be monitored more frequently at the beginning of treatment, but testing intervals can be resumed to normal after the INR has become stable.4

Head to head trials have determined liraglutide has the greatest A1c reduction and weight loss compared to others in the class.5 Dulaglutide was shown to be non-inferior to liraglutide, but weight loss was greater with liraglutide. Its dosing schedule may not be as convenient as the newer agents, but a difference in patient satisfaction was not identified between the weekly and daily agents.5

The class of GLP-1 agonists can play a vital role in the treatment of T2DM. Modest A1c reduction, weight loss, and low rates of hypoglycemia are benefits for its use in therapy. Route of administration and GI side effects may discourage patients from trying these medications. Many patient factors including desired A1c reduction, side effects, and dosing schedule should be evaluated before making a decision on an agent in this class. Liraglutide has been the most prescribed medication in this class in Wyoming Medicaid patients, which appears to be appropriate based on A1c reduction and weight loss.

References:

New P & T Committee Members

We welcome 3 new P & T Committee members: Scott Johnston, MD, Paul Johnson, MD, and Chris Mosier, RPh. Dr. Johnston joined the P & T Committee in May 2016 and Dr. Johnson and Chris Mosier joined in August 2016.

Dr. Scott Johnston practices occupational medicine in Northwest Wyoming. Dr. Paul Johnson is an otolaryngologist practicing in Cheyenne. Chris Mosier is an inpatient and critical care pharmacist practicing in Casper.
The P&T Committee met for its quarterly business meeting on August 11, 2016.

Highlights of this meeting include:

Ocaliva will require a trial and failure of ursodiol in the last year as well as a diagnosis of primary biliary cholangitis prior to approval.

Epclusa will be preferred for treatment of Hepatitis C. Class criteria applied to all Hepatitis C treatments can be found at http://www.wymedicaid.org/pa.

Zinbryta will be non-preferred in the multiple sclerosis category, requiring trial and failure of two agents from different classes. This requirement is in line with its labeled indication as it has significant safety concerns requiring a REMS program.

Nuplazid and Xiidra will be limited to indication.

A review of the pregnancy narcotic program was given. Approximately 40 pregnant patients are identified each year on chronic narcotic therapy or exhibiting signs of doctor shopping. Since the program started in 2011, twenty four babies have been identified with a diagnosis of drug addiction or withdrawal at birth. Seven of the mothers were not on Medicaid prior to delivery. Seven had no narcotics in their drug profile prior to delivery. Five were receiving narcotics from their obstetric provider and letters were sent to the narcotic provider and obstetric provider on the remaining five cases.

The proposed prior authorization criteria will be posted for public comment at www.uwyo.edu/DUR. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to October 1, 2016 for prior authorization criteria.

The next P&T Committee meeting will be held November 10, 2016 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>A1c Reduction</th>
<th>Weight Loss</th>
<th>Administration Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albilutide (Tanzeum)</td>
<td>Weekly</td>
<td>~1%</td>
<td>~1 kg</td>
<td>Reconstitute 15 minutes before injecting for 30 mg dose, and 30 minutes before for 50 mg dose</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity)</td>
<td>Weekly</td>
<td>~1.5%</td>
<td>~2.5 kg</td>
<td>No mixing needed</td>
</tr>
<tr>
<td>Exenatide (Byetta)</td>
<td>Twice daily</td>
<td>~1%</td>
<td>~2 kg</td>
<td>Inject 60 minutes before meals. No mixing needed</td>
</tr>
<tr>
<td>Exenatide (Bydureon)</td>
<td>Weekly</td>
<td>~1.5%</td>
<td>~2.5 kg</td>
<td>Reconstitute before administering</td>
</tr>
<tr>
<td>Liraglutide (Victoza)</td>
<td>Daily</td>
<td>~1.5%</td>
<td>~2.5 kg</td>
<td>No mixing needed</td>
</tr>
</tbody>
</table>
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