Ophthalmic mast cell stabilizer/antihistamines (MCS/AH) products are second-line treatments for seasonal allergic conjunctivitis (AC). Currently, there are 4 MCS/AHs available: azelastine, epinastine, ketotifen, and olopatadine. However, it is unknown which product is the best treatment option.¹

MCS/AHs do not cause rebound congestion with prolonged use (> 3 days), unlike first-line antihistamine/decongestion products.¹² Ophthalmic MCS/AHs block histamine-1 receptors and inhibit the release of histamine from mast cells. Histamine receptor blockage occurs instantly, but preventing mast cell degranulation may take up to 2-4 weeks.²³ This dual approach decreases the signs and symptoms of AC, such as redness, mucus production, tearing, and itching. Alleviation of AC by medication is assessed with the conjunctival allergen challenge test (CAC). In the CAC, an allergen is placed into the eye, and itch scores (0-4) are reported every 30 seconds for 20 minutes. The CAC allows for a quantifiable subjective measurement of itching response when a known amount of allergen is applied to the conjunctiva.²

In a double-blind study, olopatadine was more effective than azelastine in the treatment of 111 patients with AC.⁴ All patients received a CAC test prior to one dose of study medication. Patients were randomized into one of 3 treatment groups: placebo in 1 eye and azelastine in the contralateral eye; placebo in 1 eye and olopatadine in the contralateral eye; or azelastine in 1 eye and olopatadine in the contralateral eye. Less itching was reported with olopatadine (p<0.05). The authors concluded that olopatadine was more effective than azelastine in the prevention of itch following the CAC test. Limitations of this study included funding from the manufacturer of olopatadine and the short duration of treatment since it may take 2 weeks for full efficacy to occur.⁴

In another study involving 32 patients, olopatadine was more effective than ketotifen using the CAC.⁵ Olopatadine reduced itch scores more than ketotifen (p<0.05). Patients also rated the comfort level at instillation of the medication, and 76% of patients preferred olopatadine over ketotifen. The authors concluded that olopatadine was more effective and more comfortable upon instillation than ketotifen for the treatment of AC. Limitations included the short duration of the study and the possibility of bias from the manufacturer who conducted the study.⁵

Olopatadine, ketotifen, and epinastine were equally efficacious in preventing redness and itch in AC.⁵ Emedastine (antihistamine) and fluorometholone (corticosteroid) were also included in this double-blind study. One hundred patients with a history of AC were randomized into 1 of 5 treatment groups to receive 1 drop of medication in 1 eye and a drop of placebo contralaterally twice a day for 14 days. Itching, conjunctival redness, and tearing were assessed daily by patients, while investigators examined chemosis and eyelid swelling on days 7 and 14. Itch scores were lower with all medications compared to placebo (p < 0.05). Fluorometholone was the least efficacious, but the rest were equally effective in treating AC. Limitations of this study included a small sample size and the inclusion of medications from different drug classes.⁵

The evidence in the current literature has not determined which ophthalmic MCS/AH agent is best for treating AC. Olopatadine was more effective than azelastine, but ketotifen, olopatadine, and epinastine appear to have similar efficacy. Until head-to-head studies with adequate sample sizes and treatment duration have been conducted, the preferred ophthalmic MCS/AH agent is unknown.

By Dustin Cavanaugh, PharmD Candidate
(References on Page 5)
Pramipexole and Heart Failure

Pramipexole is a non-ergot dopamine agonist used to treat Parkinson’s disease (PD) and restless leg syndrome (RLS). A safety alert was issued by the FDA on September 29, 2012, about the possible increase in risk of heart failure (HF) with the use of pramipexole. Observational studies have reported a higher incidence of HF in patients taking pramipexole. However, the FDA did not request that healthcare providers discontinue the use of pramipexole because the risk of HF in these studies was not statistically significant.¹

A case-control study investigated the risk of HF in patients on dopamine agonists (DAs) and levodopa (L-dopa) for PD.² Records from 25,459 patients were reviewed. Of these, 11,151 patients were new users of DAs while 14,308 were new users of L-dopa. Control patients were matched with cases based on age and sex. The average age of all patients in the study was 80 years. Patients were followed for 2.7 years in the DA group and 3 years in the L-dopa group. DAs used by patients in the study were cabergoline, pergolide, bromocriptine, pramipexole (n=3969), and ropinirole.²

DA and L-dopa users had similar risks of HF. The use of pramipexole alone significantly increased the risk of HF (adjusted OR 1.61; 95% CI 1.09-2.38) compared to other individual agents. The first 3 months of treatment with pramipexole were associated with an increased risk of HF (adjusted OR 3.06; 95% CI 1.74-5.39), and the risk was eliminated if the treatment was discontinued (adjusted OR 0.86; 95% CI 0.59-1.26). Sensitivity analyses found no increased risk with pramipexole or other agents in patients less than 80 years of age (adjusted OR 1.29; 95% CI 0.74-2.22); however, the risk with pramipexole increased significantly in patients ≥ 80 year of age (adjusted OR 3.30; 95% CI 1.62-7.13).²

The authors concluded that pramipexole significantly increased the risk of HF in patients with PD, especially in the first 3 months of treatment. Limitations included differences between prescribing guidelines in the study countries, the observational study design, the variability of risk estimation in the different databases, the small number of cases using pramipexole (n=31), and the potential for confounding due to the effects of PD.²

Another case-control study assessed heart failure in patients with PD taking DAs (bromocriptine, cabergoline, lisuride, pergolide, pramipexole, ropinirole, rotigotine). Control patients were matched with cases based on diagnosis, age, sex, treatment history, and cohort entry date. A total of 26,814 patients treated for PD were reviewed, and the average age of patients was 80 years. Mean follow-up period was 3.4 years, during which 783 patients developed HF (8.7 cases per 1000 person-years). The HF rate increased in patients taking DAs compared to patients not taking DAs (RR 1.58; 95% CI 1.26-1.96). The risk of HF increased with the administration pramipexole (RR 1.86; 95% CI 1.21-2.85) and cabergoline (RR 2.07; 95% CI 1.39-3.07). The HF risk was independent of pramipexole dose and duration. However, only 32 case patients were taking pramipexole. After adjusting for variability in covariates, pramipexole did not significantly increase the risk of heart failure (RR 1.28; 95% CI 0.82-2.00) compared to all other DAs.³

The authors concluded that pramipexole and cabergoline significantly increased the risk of heart failure. However, the study failed to rule out the possibility that other DAs may also increase the risk of HF. Limitations of the study included the small number of cases on pramipex-ole, possible misclassification errors, and the potential confounding from the PD.³

The risk of HF was increased with pramipexole for PD in case-control studies. However, the results of these studies should be interpreted with caution because only a small number of patients with PD and HF were taking pramipexole. It cannot be stated with certainty that the increased risk of heart failure was due to the use of pramipexole and not the natural course of PD. Long term, prospective studies comparing pramipexole to other medications for the treatment of PD are needed to evaluate the effects of pramipexole on the heart.

By Ayesha Ather, PharmD Candidate

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What is IBS?
Irritable bowel syndrome (IBS) affects approximately 10-20% of Americans. Described as a “spastic bowel,” the cause of IBS is unknown. IBS symptoms cause abdominal pain, diarrhea, and/or constipation. Although IBS symptoms are usually mild, IBS can significantly lower quality of life. According to one survey, almost 70% of people with IBS were distressed by the symptoms and almost 60% felt they lacked control over their lives due to IBS.

Dietary Changes
Diet is important for controlling IBS symptoms. Symptoms are often triggered by certain foods like chocolate, milk products, beans, alcohol, sugarless gums containing sorbitol, and fatty foods. One way to manage IBS symptoms is to introduce different foods into the diet one at a time. This could reveal foods that trigger IBS symptoms and allow patients to avoid those foods to decrease symptoms.

Recently, the low FODMAP diet has gained popularity for patients with IBS. FODMAPs are short chains of carbohydrates. Foods high in FODMAPs include wheat products, cabbage, onion, dairy products, and sweeteners. Eating foods high in FODMAPs can increase gas and discomfort, which can lead to abdominal pain and bloating.

Large fatty meals seem to aggravate IBS symptoms by triggering diarrhea. Eating small, low-fat meals throughout the day may help manage IBS symptoms.

Over-the-Counter Medications
Patients with IBS often use over-the-counter (OTC) medications to treat their symptoms. IBS treatment with OTC products should be specific to the patient’s symptoms. The following OTC items may be helpful in relieving IBS symptoms.

Fiber
Fiber can be beneficial in patients with constipation. Fiber relieves constipation by bulking up and softening stools. Fiber also normalizes bowel movements, which may be helpful in patients with diarrhea symptoms. Metamucil® (psyllium), Citrucel® (methylcellulose), or other bulk-forming laxatives can help relieve constipation. Because fiber can cause bloating, gradually increasing the amount over several weeks to the recommended daily dose is suggested.

Loperamide
Imodium® (loperamide) may be an effective first choice for patients with IBS suffering from diarrhea. Loperamide slows down bowel movements, allowing more water to be absorbed from the stool. Infrequent side effects of loperamide include constipation, abdominal pain, dry mouth, nausea, and vomiting. Loperamide should not be used continuously but as needed to reduce the risk of constipation or other side effects.

Calcium
Calcium has been helpful in providing symptom relief in patients with diarrhea due to IBS. Constipation is one side effect of calcium supplementation. Although calcium has not been studied to treat diarrhea due to IBS, it has been used successfully in patients with IBS and diarrhea.

Peppermint Oil
Peppermint oil can decrease abdominal pain and discomfort in patients suffering from IBS. Peppermint oil helps relieve abdominal pain by decreasing muscle spasms in the gut. Enteric-coated capsules are recommended since the coating minimizes heartburn from peppermint oil.

Probiotics
IBS may be triggered by an imbalance in gut bacteria. By restoring the balance with probiotics, IBS symptoms decreased in many studies. Align®, VSL #3®, and Lacteol Fort® were used in clinical studies. These products contain either a combination or single strains of different probiotics such as *Lactobacillus* and *Bifidobacteria*. However, no specific probiotic product is recommended over others.

Although IBS can be debilitating in some patients, there are many ways to manage IBS symptoms. In addition to OTC medications and diet, cognitive behavioral therapy or hypnosis may be effective in managing IBS symptoms. Exercise activities that reduce stress such as yoga can also help patients with IBS. Because there are many ways to manage IBS symptoms, patients should talk with their primary care providers before starting OTC medications or supplements, changing diet, or starting new exercise regimens.

By Chris Chong, PharmD Candidate

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(References continued on Page 5)
Zero-calorie sweeteners (ZCS) are FDA approved food additives that are considered to have little to no calories or other nutrients. The average American consumes 22 teaspoons of sugar a day (nearly three times the recommended amount), which is 355 calories/day or approximately 37 pounds of weight gain per year. Over the past several years artificial sweeteners have been promoted as a healthier alternative to sugar. The FDA has established acceptable daily intake (ADI) levels for each sweetener. According to the FDA, ADI is the amount of artificial sweetener an average person can ingest daily without significant health risk. The table below lists the recommended amounts of ZCS.

One of the problems with all ZCS is that they are not calorie-free and they contain carbohydrates. According to the FDA, low-calorie beverages contain 40 or less calories per serving size and zero-calorie beverages contain less than 5 calories per serving size. Diet soda labels may state zero-calories, but they may still contain less than 5 calories in a 12 oz. can. A 64 oz. zero-calorie soda can contain up to 22 calories. If an individual drinks 64-oz. of soda each day, this can lead to a 2.5 pound weight gain in a year.

Low-calorie foods and calorie-free drinks may help people control their blood sugar levels or weight. However, individuals may end up consuming more foods and beverages (diet soda or juice) to compensate for a low-calorie diet, not realizing that they are eating more calories than they think.

Stevia and aspartame may help people control their appetite and blood sugar levels. In one study, healthy people who ate food containing stevia or aspartame did not eat more food, still felt full, and decreased their blood sugar and insulin levels compared to people who ate food with sugar.

ZCS may not be able to control blood sugar levels if consumed in higher than recommended quantities. People with type 2 diabetes who consumed large amounts of sucralose were not able to maintain their blood sugar levels, insulin levels, and glycated hemoglobin (HbA1c). HbA1c is a blood test that measures blood sugar levels for the previous 3 months.

Zero-calorie sweeteners can help satisfy a consumer’s sweet cravings without adding calories. However, zero-calorie products do contain some calories and carbohydrates. People who track daily calorie and carbohydrate counts to manage their weight or control their blood sugar levels need to include zero-calorie products in these counts.

By Ayesha Ather, PharmD Candidate

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### Zero-calorie sweeteners

<table>
<thead>
<tr>
<th>Sweetener</th>
<th>Brand Name</th>
<th>Acceptable Daily Intake</th>
<th>Number of 12-oz. servings per ADI for 150 lb person</th>
<th>Amount in one packet (equal to 2 Tbs.)</th>
<th>Number of packets per ADI for 150 lb person</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acesulfame-K</td>
<td>Sweet One</td>
<td>15 mg/kg (7 mg/lb)</td>
<td>25</td>
<td>50 mg</td>
<td>20</td>
</tr>
<tr>
<td>Aspartame</td>
<td>Equal, Nutrasweet</td>
<td>40 mg/kg (18 mg/lb)</td>
<td>14</td>
<td>40 mg</td>
<td>68</td>
</tr>
<tr>
<td>Saccharin</td>
<td>Sweet’N Low</td>
<td>5 mg/kg (2 mg/lb)</td>
<td>42</td>
<td>40 mg</td>
<td>8.5</td>
</tr>
<tr>
<td>Sucralose</td>
<td>Splenda</td>
<td>5 mg/kg (2 mg/lb)</td>
<td>15</td>
<td>11 mg</td>
<td>30</td>
</tr>
<tr>
<td>Stevia</td>
<td>Truvia, PureVia, Sweet Leaf</td>
<td>2 mg/kg (0.9 mg/lb)</td>
<td>16</td>
<td>9 mg</td>
<td>30</td>
</tr>
</tbody>
</table>

ADI=Acceptable Daily Intake

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