Attention-deficit/hyperactivity disorder (ADHD) involves hyperactivity, impulsivity, and inattention and affects roughly 4.4% of adults in the United States. While pharmacologic intervention is the mainstay of therapy for ADHD, alternative treatments are sought due to the lack of patient response and compliance with the required medication regimens. This randomized, single-blind, active-controlled trial evaluated the efficacy of cognitive behavioral therapy (CBT) in refractory patients with ADHD already stabilized on psychotropic medications.

Eighty-six patients were randomized to receive twelve, 50-minute sessions of either individual CBT (n=43) or relaxation with educational support (control group; n=43). Subjects in the CBT group received psychoeducation modules regarding ADHD and were taught skills to lessen distractibility, while the control group received training in progressive muscle relaxation. Patients were evaluated at baseline, post-treatment (approximately 15 weeks), 6 months, and 12 months using the Clinical Global Impression (CGI) scale for severity and ADHD rating scale. Patients with at least a 30% reduction on the ADHD scale or a two-point reduction on the CGI scale were considered treatment responders.

Patients in the CBT group had significantly lower post-treatment scores (improved ADHD symptoms) on the ADHD rating scale (estimated parameter for treatment effect, -4.63 [95% CI, -8.30 to -0.96]) and Clinical Global Impression scale (estimated parameter for treatment effect, -0.53 [95% CI, -1.01 to -0.05]) compared to the control group. Using the CGI scale, more responders were found in the CBT group compared to the control group (53% vs 23%; OR 3.8, 95% CI 1.5 to 9.59; p=0.01). Similar rates of responders were found in both groups using the ADHD rating scale (67% vs 33%; OR 4.29, 95% CI 1.74 to 10.58; p=0.002). Although statistically insignificant, there was evidence of maintained gains over 6 and 12 months in the CBT responders. The study had missing data due to inconsistent patient follow-up, which may have produced inaccurate results. Additionally, the ability to generalize results to patients in practice may be limited because their motivation for treatment may be different than that in patients involved in the trial.

SUMMARY: The use of CBT in patients with persistent ADHD symptoms while maintained on psychotropic medications was effective in improving ADHD symptoms compared to relaxation with educational support.


By Jodi Moffit, Pharm.D. Candidate
Multiple sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system and is often characterized by relapsing-remitting symptoms, including fatigue, ataxia, paresthesia, and difficulty walking. Several medications are used to decrease exacerbations in patients with relapsing/remitting MS, including interferon beta-1a, interferon beta-1b, glatiramer acetate, and mitoxantrone. Despite therapy with these agents, the majority of patients experience disease progression. Amynra® (dalfampridine extended release) is a potassium-channel blocker approved in January 2010 as the first medication indicated to improve walking in patients with MS.

A double-blind, placebo-controlled study investigated the dose-related safety and efficacy of up to 40 mg twice daily of dalfampridine ER in patients with MS. Eligible patients were 18-60 years old with an Expanded Disability Status Scale (EDSS) score < 6.5 and a Fatigue Severity Score (FSS) > 4.0. Patients with an MS exacerbation within 60 days prior to the study, a history of seizures, a history of cancer in the previous five years, and any change in concurrent interferon or glatiramer within the previous three months were excluded. Following a four-week baseline period, subjects were randomly assigned to receive either dalfampridine ER 10 to 40 mg twice daily, increasing in 5 mg increments weekly (n=25), or placebo (n=11) for eight weeks. The primary endpoint was the relative safety of different doses of dalfampridine (10, 15, 20, 25, 30, 35, and 40 mg twice daily). Secondary endpoints included changes in the LEEMT score and Ashworth score for spasticity. The dalfampridine patients had a 25.2% improvement in walking speed compared to a 4.7% improvement in the placebo group (treatment difference of 20.5%, 95% CI 21.5% to 28.8%; p<0.001). The average improvement in the LEMMT score was 0.18 for the dalfampridine group versus 0.04 for the placebo group (p=0.0002). There was no significant difference in the average Ashworth scores between groups. The authors concluded that dalfampridine improved walking ability in some people with MS and provided a clinically meaningful therapeutic benefit. Limitations included the small study population and possible financial conflicts of interest.

Dalfampridine will likely be used as adjunctive therapy to agents that modify disease progression in some patients with MS. The maximum recommended dose is 10 mg twice daily taken 12 hours apart.

Modest improvements in walking speed were seen compared to placebo in two randomized, placebo-controlled studies.

The most common adverse effects associated with dalfampridine include urinary tract infection (12%), insomnia (9%), dizziness, headache, nausea, and asthenia (each 7%).

References:
*Clostridium difficile* is a spore-forming, Gram-positive, anaerobic bacillus and is the most frequent cause of hospital-acquired diarrhea. Although initial response rates to standard antibiotic therapy with vancomycin or metronidazole for *Clostridium difficile*-associated diarrhea (CDAD) exceeds 90%, up to 30% of patients experience recurrent CDAD, often leading to re-hospitalization, increased medical costs, and mortality. Complications of recurrent CDAD include toxic megacolon, *Clostridium difficile*-associated arthritis, and sepsis.\(^1\) Risk factors for recurrent CDAD include advanced age, chronic renal failure, multiple episodes of previous CDAD infection, and high white blood cell counts (≥15 X 10^9). Recent literature suggests that the use of gastric acid blocking drugs, especially proton pump inhibitors (PPIs), could be associated with CDAD recurrence.\(^2\)

A retrospective chart review was conducted at Seoul National Hospital for all patients with the diagnosis of CDAD from January 2006 to December 2007.\(^3\) The study attempted to determine the risk factors for recurrent CDAD in hospitalized patients and to study the relationship between recurrent CDAD and PPIs. A total of 125 patients (mean age, 67.6 ± 13.9 years) were included in the study and all had a positive ELISA test for *Clostridium difficile* toxins A and B, along with three or more stools per day, abdominal pain, fever, and leukocytosis at least three days after admission. Patients were excluded if they were under 18 years of age, had CDAD in the previous three months, failed to complete at least seven days of antibiotic therapy, had another contagious pathogen, or had inflammatory bowel disease. Of the 125 patients, 27 (21.6%) experienced recurrent CDAD within 90 days of initial CDAD, and 98 (78.4%) did not have recurrent CDAD.\(^2\)

The investigators determined the risk factors for recurrent CDAD to include age >65 years old (adjusted OR 1.32, 95% CI 1.12 to 3.87; \(p=0.031\)), low serum albumin level <2.5 g/dL (adjusted OR 1.85, 95% CI 1.35 to 4.91; \(p=0.028\)), and use of PPIs at least three days before CDAD diagnosis and continuously thereafter (adjusted OR 3.48, 95% CI 1.64 to 7.69; \(p=0.016\)).\(^2\) Fifty-six (44.8%) of the patients received PPIs: 17 in the recurrent CDAD group (63%) and 39 in the non-recurrent group (39.8%). Gender, length of hospital stay, duration and type of antibiotic therapy, severity of the first episode of CDAD, the presence of diabetes mellitus or renal failure, leukocyte count, and C-reactive protein levels were not associated with an increased risk for recurrent CDAD. This study was limited by its retrospective design and by the small patient population. Additionally, stool cultures were not conducted to verify if the infections were recurrences or relapses of infection never fully cured. Adherence to PPI regimens could not be verified and may have led to overestimation of continued PPI use.\(^2\)

How PPIs may increase the risk of CDAD is not completely understood, although a few mechanisms have been proposed. Although *Clostridium difficile* spores are considered to be resistant to stomach acid, spore growth and survival may be greater in a higher pH environment. It has also been proposed that PPIs decrease the immune response in the gastrointestinal tract, leading to increased bacteria colonization and subsequent CDAD.\(^2\)

This is the largest study to date looking at PPI use and recurrent CDAD. Of the significant risk factors for recurrent CDAD identified in this study, the use of PPIs is modifiable. Limiting the concomitant use of PPIs in patients with CDAD may reduce the risk of recurrent CDAD. Further studies are needed to understand the relationship between recurrent CDAD and PPI use and to determine whether only PPIs increase the risk of recurrent CDAD or if all agents that reduce stomach acidity increase the risk.

By Michael Harrington, Pharm.D. Candidate

References:
Exenatide vs. Pioglitazone vs. Sitagliptin as Step-2 Antidiabetic Therapy with Metformin Background

According to the American Diabetes Association (ADA), appropriate lifestyle changes and metformin are the first steps in treating patients with type 2 diabetes without contraindications. If this intervention does not decrease glycosylated hemoglobin (A1c) to less than 7%, the addition of basal insulin, a sulfonylurea, a thiazolidinedione (e.g., pioglitazone), or a GLP-1 agonist (e.g., exenatide) should be tried. Because the ADA stresses the importance of minimizing hypoglycemic episodes and weight gain, this study used newer treatments known to improve glycemic control as well as help correct metabolic abnormalities associated with diabetes, such as obesity, hypertension, and dyslipidemia. The DURATION-2 trial compared the efficacy, safety, and tolerability of three validated step-two drugs: pioglitazone, exenatide, and sitagliptin, a DDP-4 inhibitor.

This 26-week, double-blind, double-dummy trial included 491 patients with type 2 diabetes. All patients were otherwise healthy and were stable on metformin for at least two months prior to screening, had an A1c of 7.1% to 11.0%, and had a body-mass index of 25-45 kg/m². Trial participants received either exenatide 2 mg injected once weekly plus oral placebo once daily, placebo injected once weekly plus 100 mg sitagliptin once daily, or placebo injected once weekly plus 45 mg pioglitazone once daily. The primary endpoint was the change in A1c from baseline to week 26. There were 15 secondary endpoints which included proportion of patients achieving target A1c of 7.0% or lower and changes in fasting plasma glucose (FPG), body weight, lipid profile, and blood pressure.

Exenatide reduced A1c by an average of -1.5% (95% CI -1.7 to -1.4%), which was a significantly greater reduction than pioglitazone (-1.2%, 95% CI -1.4 to -1.0%; p=0.0165) or sitagliptin (-0.9%, 95% CI -1.1 to -0.7%; p=0.0001).

Among participants with a baseline A1c of 9.0% or higher, exenatide improved A1c by 2.0% (95% CI -2.4 to -1.6%), compared to improvements of 1.5% with pioglitazone (95% CI -1.9 to -1.1%; p=0.0436) and 1.3% with sitagliptin (95% CI -1.7 to -0.9%; p=0.0071). Significantly more exenatide patients (59%) achieved an A1c of 7.0% or lower compared to pioglitazone patients (43%; p=0.0015) or sitagliptin patients (30%; p=0.0001). Exenatide was superior to sitagliptin in lowering FPG (treatment difference -0.9 mmol/L, 95% CI -0.3 to -1.4 mmol/L; p=0.0038), body weight (treatment difference -1.5 kg, 95% CI -2.4 to -0.7 kg; p=0.0002), and systolic blood pressure (treatment difference -4 mmHg, 95% CI -6 to -1 mmHg). Exenatide was superior to pioglitazone in lowering body weight (treatment difference -5.1 kg, 95% CI -5.9 to -4.3 kg; p<0.0001). Pioglitazone was superior to exenatide in raising HDL cholesterol (treatment difference 0.11 mmol/L, 95% CI 0.07 to 0.15 mmol/L; p<0.0001) and lowering triglycerides (treatment difference of -5%, 95% CI -11 to 0%). Exenatide showed a greater incidence of nausea (24%), vomiting (11%), and diarrhea (18%) compared to sitagliptin (10%, 2%, and 10%, respectively) and pioglitazone (5%, 3%, and 7%, respectively). Episodes of hypoglycemic events were similar between groups. This trial did not compare the studied medications to basal insulin or sulfonylureas, which are step-two medication therapies that have more supporting evidence. The trial is further limited because long-term outcomes such as mortality and cardiovascular disease were not assessed.

SUMMARY: The use of exenatide was associated with a greater reduction in A1c compared to pioglitazone and sitagliptin, especially in patients with a baseline A1c of 9.0% or greater. Exenatide was also superior in lowering body weight but was associated with more nausea, vomiting, and diarrhea.

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