PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Plecanatide: New Indication

The FDA has approved plecanatide (*Trulance*) for treatment of irritable bowel syndrome with constipation (IBS-C) in adults. The agent was previously indicated only for chronic idiopathic constipation.

In clinical trials, patients who took plecanatide experienced significant reductions in abdominal pain, as well as improvements in stool frequency, stool consistency, and straining with bowel movements. In these trials, rates of response (both a ≥30% reduction in worst abdominal pain and an increase of ≥1 complete spontaneous bowel movements from baseline for ≥6 weeks) with plecanatide ranged from 22% to 30%. Diarrhea was the most common adverse effect of plecanatide treatment, affecting about 4% of treated patients, and was severe in 1%. Plecanatide is contraindicated in patients aged <6 years and should be avoided in patients aged <18 years.

Plecanatide (*Trulance*) Gets FDA Nod for IBS With Constipation in Adults. Medscape: Jan 26, 2018. Available at https://www.medscape.com/viewarticle/891839.

Erenumab for Episodic Migraine

In a phase III placebo-controlled trial, erenumab reduced migraine frequency in patients with episodic migraine.

Background: Episodic migraine, defined as <15 migraine days per month, affects about 90% of migraine sufferers. Currently used preventive medications were developed for other indications and are not targeted to the specific pathways involved in migraine. Erenumab is a monoclonal antibody antagonist to the calcitonin gene-related peptide receptor, a pathway involved in nociceptive mechanisms believed to be important in migraine.

Methods: Study participants (n=955) were adults with a ≥12-month history of episodic migraine, with 4–14 migraine days per month. Patients concomitantly using stable doses of most other migraine-prevention medication were included. However, those who had received a botulinum toxin injection in the previous 4 months or who had received ergotamine derivatives, steroids, or triptans in the previous 2 months were excluded. After a 4-week observation phase, patients were randomly assigned to receive monthly subcutaneous injections of 70 mg or 140 mg erenumab or placebo in a double-blind fashion for 6 months. Headaches were self-reported in an electronic diary, and the primary outcome was change in the mean number of migraine days per month from baseline to the last 3 months of treatment. Secondary endpoints included a ≥50% reduction in migraine frequency and reduction in the use of acute migraine medications.

Results: A total of 858 patients (90%) completed the 6 months of double-blind treatment. At baseline, patients had an average of 8.3 migraine days per month and about 3% were using other migraine-preventive medications concomitantly. Nearly 40% had discontinued previous migraine preventive medication because of intolerance or lack of efficacy.

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Both doses of erenumab were associated with significantly larger mean reductions in migraine days than placebo: 3.2 and 3.7 days, respectively, compared with 1.8 days with placebo ($p<0.001$ for both comparisons). About half of patients in the erenumab groups had a ≥50% reduction in monthly migraine days, compared with 27% of the placebo group ($p<0.001$). Use of acute migraine medications was also reduced to a greater degree. Patients in the erenumab groups also reported reduced interference of migraine with their daily lives, relative to the placebo group.

The frequency of most adverse events did not differ between erenumab and placebo, with the exception of injection-site pain, which affected 11 erenumab-treated patients and 1 placebo-treated patient. Serious medication-related adverse effects were uncommon. There were no between-group differences in hepatic-function, creatinine levels, total neutrophil counts, vital signs, or electrocardiographic findings.

Discussion: These results, while preliminary, support the short-term preventive effects of erenumab on episodic migraine. Following the acute double-blind phase, patients in the study were eligible to participate in an open-label extension study; these results will be reported separately.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Goadsby P, et al: A controlled trial of erenumab for episodic migraine. *NEJM* 2017;377 (November 30):2123–2132. From King's College Hospital, London, U.K.; and other institutions. **Funded by Amgen and Novartis. Nine of 10 study authors disclosed financial relationships with commercial sources including Amgen and/or Novartis; the remaining author declared no competing interests.**

***See Reference Guide.**

Loperamide Packaging Limits

The over-the-counter antidiarrheal opioid receptor agonist loperamide (*Imodium*) is being used increasingly to self-medicate for opioid withdrawal and, less frequently, to achieve opioid psychoactive effects.[1] Using higher than recommended doses of loperamide can result in serious cardiac adverse events, including QT interval prolongation, Torsades de pointes or other ventricular arrhythmias, syncope, and cardiac arrest. Despite warnings issued in 2016, the FDA continues to receive reports of serious cardiac effects and deaths with much higher than the recommended doses of loperamide, primarily in patients misusing the product. In an effort to support safe use of loperamide, the FDA has requested the manufacturers use blister packs or other single-dose packaging and to limit the number of doses in each package.[2]

[1]Stanciu C, Gnanasegaram S: Loperamide, the "poor man's methadone": brief review. *Journal of Psychoactive Drugs* 2016; doi 10.1080/02791072.2016.1260188. See *Primary Care Drug Alerts* 2017;38 (January):3–4.

[2] FDA Drug Safety Communication: Imodium (loperamide) for Over-the-Counter Use: FDA Limits Packaging To Encourage Safe Use. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm594403.htm.

Statins and Diabetes

According to results of a secondary analysis of a clinical trial of diabetes-prevention interventions, statin therapy is associated with a 30% increase in type 2 diabetes incidence in high-risk individuals. The evidence suggests glucose status should be monitored and healthy behaviors should be encouraged in patients at high risk for diabetes who are taking statins.

Methods: Data were analyzed from the Diabetes Prevention Program (DPP) and the subsequent DPP Outcomes Study (DPPOS). Participants were >3200 overweight adults with impaired glucose tolerance who did not meet criteria for diabetes based on fasting plasma glucose levels. Patients were randomly assigned to intensive lifestyle intervention, metformin (*Glucophage*), or placebo for about 3 years, followed by additional lifestyle programs or open-label metformin for an additional 7 years. Lipid-lowering medications were prescribed by each patient's own physician, outside of the study protocol, and use was ascertained every 6 months based on self-report. The primary study outcome was diabetes onset, determined by an annual oral glucose tolerance test or a semiannual fasting plasma glucose tolerance test with confirmation by a second test.

Results: Statin use in study participants increased from about 4% at baseline to 35% after 10 years, with similar proportions in the 3 treatment groups. Patients taking statins were older, more likely to be male, and had modestly higher baseline levels of fasting plasma glucose and HbA1c and a lower insulinogenic index. The hazard ratio* for diabetes onset with statin use in the pooled cohort was 1.36. Risk was attenuated only slightly to 1.27 with adjustment for multiple confounding factors including baseline diabetes risk and indication for statin use. Statin dosage

was not measured, but diabetes risk did not differ in patients taking high- versus low-potency statins; nor was risk associated with change in LDL-cholesterol levels.

Discussion: This analysis suggests that the indications for statin therapy or a higher level of baseline diabetes risk factors are not a major influence on statin-associated diabetes risk. The mechanisms linking statins with diabetes onset are not clear.

Crandall J, et al: Statin use and risk of developing diabetes: results from the Diabetes Prevention Program. *BMJ Open Diabetes Research & Care* 2017; doi 10.1136/bmjdrc-2017–000438. From Albert Einstein College of Medicine, Bronx, NY; and other institutions. **Funded by the National Institute of Diabetes and Digestive and Kidney Diseases; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Statins and Erectile Dysfunction

Results of a meta-analysis that included nearly 70,000 men with cardiovascular disease or risk factors indicate that statin therapy is not associated with increased onset of erectile dysfunction.

Background: A potential link between statin use and erectile dysfunction was suspected because statins are known to reduce testosterone levels. The association was supported by case reports, post-marketing studies, and case-control studies but was not validated in 2 recent propensity score-matched cohort studies.

Methods: A literature search identified randomized controlled trials and observational studies of statins that reported new onset of erectile dysfunction in men with established cardiovascular disease or cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, and elevated C-reactive protein levels. A total of 6 studies—3 randomized trials and 3 observational studies, with a total of nearly 70,000 patients—were included in the meta-analysis. The average follow-up was 3.5 years, and about one third of patients were statin users. All but 1 of the studies had a low risk of methodologic bias, and there was no evidence of publication bias.

Results: Compared with non-use, statin use was not associated with new-onset erectile dysfunction, which affected 5% and 4% of the groups, respectively (relative risk,* 0.96). No effects were observed in subgroup analyses of randomized trials versus observational studies, large versus small studies, or the 4 studies in which erectile dysfunction was the primary outcome. The analysis found that the effect of statins did not differ according to patient age or presence of diabetes. Analyses based on the type of statin (i.e., hydrophilic or lipophilic) were not conducted due to limited data.

Discussion: Although statins lower testosterone levels, they do not appear to induce erectile dysfunction and may actually have effects that protect against it. The drugs may counteract LDL-cholesterol-related oxidative injury and vascular inflammation, improving endothelial function in the penile vascular tissue and improving penile blood flow.

Study Rating*—18 (100%): This study met all criteria for a systematic review/met-analysis.

Elgendy A, et al: Statin use in men and new onset of erectile dysfunction: a systematic review and meta-analysis. *American Journal of Medicine* 2017; doi 10.1016/j.amjmed.2017.10.043. From the University of Florida, Gainesville; and other institutions. **This study was conducted without funding. The authors declared no competing interests.**

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Blood Test for Concussion

The FDA has authorized marketing of the Brain Trauma Indicator, the first blood test to evaluate mild traumatic brain injury or concussion in adults. Following head injury, patients are typically evaluated using a neurological scale and CT scan. However, most of these patients are not found to have intracranial lesions. The Brain Trauma Indicator measures proteins released from the brain into blood after a head injury. Results can be available within 3–4 hours. Levels of these proteins can help predict which patients may have intracranial lesions and require CT scans, thus potentially preventing unnecessary neuroimaging and associated radiation exposure. In clinical trials, The Brain Trauma Indicator predicted the presence or absence of intracranial lesions following head injury in 97.5% and 99.6% percent of patients, respectively.

FDA News Release: FDA authorizes marketing of first blood test to aid in the evaluation of concussion in adults. New quick testing option to help reduce need for CT scans, radiation exposure for patients. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm596531.htm.

Mixed-Release Amphetamine

The newly-approved triple-bead mixed amphetamine salts SHP465 (*Mydayis*) was effective and well tolerated in a clinical trial in children and adolescents. The new formulation contains 3 types

of drug-releasing beads, providing immediate and delayed release at pH values of 5.5 and 7.

Methods: Study participants, recruited from 36 U.S. sites, were aged 6–17 years and had a primary diagnosis of ADHD, with a baseline ADHD Rating Scale-IV (ADHD-RS-IV) score of ≥28. After a washout of previous medications, patients were randomly assigned to receive double-blind treatment with 12.5 mg SHP465 or placebo, taken once daily at 7AM. At the end of the first study week, the dose was increased to 25 mg based on response and tolerability. The primary efficacy outcome, assessed after 4 weeks, was change from baseline in the ADHD-RS-IV total score. The 4-week score on the Clinical Global Impression–Improvement* scale was the key secondary endpoint.

Results: Of 264 enrolled patients, about 40% were aged ≤12 years, and 234 completed the study. The most frequent reasons for withdrawal were adverse events (11 patients receiving active treatment and 3 receiving placebo) and lack of efficacy (1 with SHP465, 4 with placebo). The optimal daily dose of SHP465 was 25 mg in 72% of patients and 12.5 mg in 24%.

At baseline, the mean total ADHD-RS-IV scores were 39 and 40 in the SHP465 and placebo groups, respectively. At the 4-week assessment, scores were reduced by 21 points with SHP465, compared with 11 points with placebo (effect size,* 0.80; p<0.001). Scores on both the hyperactivity/impulsivity and inattentiveness subscales decreased by a significantly larger extent with SHP465 than placebo (p<0.001 for both). The mean CGI-I score at week 4 was 3 for placebo and 2.2 for SHP465 (effect size, 0.65; p<0.001).

The most frequently reported adverse events with SHP465 were decreased appetite and insomnia. Of the adverse events that led to study discontinuation, 9 were related to the study drug. All were of mild or moderate severity and resolved with treatment discontinuation.

Discussion: Previously published studies have shown that SHP465 is safe and efficacious in adults. This is the first published phase III study in children and adolescents; the agent is approved for use in patients aged ≥13 years. Although efficacy cannot be compared directly, the effects of SHP465 appear similar to other long-acting stimulants. The adverse-effect profile is also consistent with other long-acting amphetamines.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Brams M, et al: SHP465 mixed amphetamine salts in the treatment of attention-deficit/hyperactivity disorder in children and adolescents: results of a randomized, double-blind placebo-controlled study. *Journal of Child and Adolescent Psychopharmacology* 2018;28 (January):19–28. From Baylor College of Medicine, Houston, TX; and other institutions including Shire, Lexington, MA. **Funded by Shire Development, LLC. All study authors disclosed financial relationships with commercial sources including Shire.**

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Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.