PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Celebrating 40 Years of Bringing Clinical Research to Practice

Novel Weight-Loss Agent Approved

The oral, non-systemic, nonstimulant, super-absorbent hydrogel *Plenity* has received FDA approval for weight management in adults with a body mass index (BMI) of 25–40 (i.e., overweight or obese). It is the only prescription weight management product approved for use by adults with a BMI as low as 25, with or without comorbidities such as hypertension, diabetes, or dyslipidemia.

The agent, intended for use in conjunction with diet and exercise, cross-links modified cellulose and citric acid to create a 3-dimensional matrix. After ingestion, *Plenity* particles rapidly absorb water in the stomach and mix with ingested foods to create thousands of small individual gel pieces with a consistency like that of solid plant-based foods but without caloric value. The *Plenity* hydrogel mass increases the volume and elasticity of the contents of the stomach and small intestine, creating a feeling of fullness and satiety. In the large intestine, the hydrogel is partially broken down and loses its 3-dimensional structure and most of its absorption capacity. The released water is reabsorbed, and the remaining cellulosic material is expelled in the feces. *Plenity* is considered a medical device because it achieves its primary intended purpose through mechanical modes of action. There is no restriction on how long *Plenity* can be used to assist in weight management.

In clinical studies, 60% of adults treated with *Plenity* lost ≥5% of their body weight and 26% achieved a ≥10% weight loss. No serious adverse effects were reported, and tolerability was similar to placebo. *Plenity* is contraindicated in patients who are pregnant and those who are allergic to cellulose, citric acid, sodium stearyl fumarate, gelatin, or titanium oxide. Use should be avoided in patients with esophageal anomalies, suspected strictures, or complications from prior GI surgery that could affect transit and motility. It should be used cautiously in patients with active GI conditions such as GERD, ulcers, or heartburn. *Plenity* may alter the absorption of medications.

Gelesis granted FDA clearance to market Plenity™—a new prescription aid in weight management [press release]. Boston, MA; Gelesis: April 14, 2019. Available at www.gelesis.com/2019/04/14/gelesis-granted-fda-clearance-to-market-plenitytm-a-new-prescription-aid-to-weight-management/.

Comparative Efficacy of Lipid-Lowering

According to the results of a network meta-analysis,* statins and PCSK9 inhibitors have similar efficacy for prevention of cardiovascular events, but lipid-lowering benefits of the PSCK9 inhibitors are stronger and they do not increase liver enzymes or risk of new-onset diabetes. Ezetimibe (*Zetia*) has smaller lipid-lowering effects than the other medications and no cardio-protective effect.

Methods: The review included randomized controlled trials published since 2000 that evaluated lipid-lowering treatment in adults followed for ≥6 weeks. The analysis examined multiple efficacy and safety outcomes in the 84 identified

studies (>246,000 patients). None of the trials directly compared medications; all investigations were placebo controlled.

Results: PCSK9 inhibitors ranked first for improving all cholesterol-related outcomes (see table), while statins ranked first in terms of cardio-vascular event prevention and mortality. All-cause mortality was similar with statins and PCSK9 inhibitors. Ezetimibe ranked as the least effective choice for all outcomes.

Effect of lipid-lowering drugs on LDL cholesterol and cardiovascular events	
Change in LDL cholesterol	**Standardized mean difference* vs placebo**
PCSK9	50.76
Statins	34.03
Ezetimibe	18.70
Change in total cholesterol	**Standardized mean difference vs placebo**
PCSK9	35.8
Statins	24.75
Ezetimibe	13.75
Cardiovascular events	**Odds ratio* vs placebo**
Statins	0.80
PCSK9	0.82
Ezetimibe	0.88

None of the medications were associated with a higher rate of severe adverse events than placebo. Only ezetimibe was linked with an increase in neurocognitive adverse events; statins were linked with a significantly lower rate compared with the other medications. Only statins were associated with increases in ALT and creatine kinase. Diabetes onset, a rare adverse event, occurred in significantly more patients receiving statins than placebo (odds ratio, 1.13).

Study Rating—16 (89%):* This study met most criteria for a systematic review/meta-analysis; however, the source of funding was not included.

Zhao Z, et al: Comparative efficacy and safety of lipid-lowering agents in patients with hypercholesterolemia: a frequentist network meta-analysis. *Medicine* 2019; doi 10.1097/MD0000000000014400. From People's Hospital of Zhengzhou University China. **Source of funding not stated. The authors declared no competing interests.**

See Reference Guide.

Flibanserin Labeling Change

At the time of its initial approval for treatment of generalized hypoactive sexual desire disorder in premenopausal women, the serotonergic drug flibanserin (*Addyi*) was required to carry a boxed warning contraindicating its use with alcohol because of the possibility for severe hypotension and syncope. Following a review of postmarketing studies, the FDA has determined that although concern still exists about alcohol consumption in close temporal association with flibanserin dosing, alcohol need not be avoided completely by women taking the drug. While the boxed warning will remain, the label will be updated to reflect that women should discontinue drinking alcohol ≥2 hours before taking flibanserin at bedtime or to skip the dose that evening. Women should not consume alcohol at least until the morning after taking flibanserin at bedtime.

FDA News Release: FDA orders important safety labeling changes for Addyi. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635847.htm.

Tamoxifen: Long-Term Survival

Long-term follow-up of a randomized trial suggests 2 years of tamoxifen treatment confers lasting survival benefits for up to 30 years in premenopausal women with estrogen receptor (ER)-positive breast cancer.

Methods: Study subjects were premenopausal women with primary stage 2 breast cancer who received 2 years of randomly assigned adjuvant tamoxifen treatment or no systemic treatment. Because women with estrogen receptor-negative status were shown not to benefit from tamoxifen, the long-term follow-up focused on the ER-positive subgroup. The primary outcome was the breast cancer-free interval (i.e., time to first local, regional, or distant recurrence, contralateral breast cancer, or breast cancer-related death).

Results: A total of 362 ER-positive women were included in the analysis. The median follow-up for patients without a breast cancer event was 28 years, and the maximum was 30 years. In the ER-positive group, tamoxifen treatment prolonged the breast cancer-free interval by 38% (hazard ratio,* 0.62; p=0.001). About 20% of first recurrences occurred after 15 years and comprised mostly distant recurrences followed by contralateral breast cancer. Significant or near-significant

positive effects were observed in ER-positive women in each 5-year interval of follow-up. Tamoxifen also reduced a composite secondary endpoint of distant recurrence and breast cancer related death (hazard ratio, 0.73; p=0.043). However, among the 165 women with ER-positive tumors who had a distant recurrence, median survival from the time of recurrence was 29 months in the tamoxifen group and 43 months in untreated women.

Discussion: These results emphasize the importance of long-term follow-up for women with a history of breast cancer. The finding of reduced survival after recurrence in tamoxifen-treated women has been previously described and warrants further investigation.

Ekholm M, et al: Effects of adjuvant tamoxifen over three decades on breast cancer-free and distant recurrence-free interval among premenopausal women with oestrogen receptor-positive breast cancer randomised in the Swedish SBII:2pre trial. *European Journal of Cancer* 2019;110:53–61. doi: 10.1016/j.ejca.2018.12.034. From Linkoping University, Sweden; and other institutions. **Funded by Futurum—the Academy of Health and Care; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Peppermint Oil for IBS

According to the results of a meta-analysis of randomized controlled trials, peppermint oil is both effective and safe in the treatment of irritable bowel syndrome.

Background: Peppermint oil has multiple mechanisms that may be helpful in IBS, including carminative, antispasmodic, antiinflammatory, immunomodulatory, and analgesic properties. Several previous meta-analyses have evaluated peppermint oil for IBS; however, most early efforts were hindered by study design flaws and inconsistent results. The present analysis was motivated in part by a recent study of a new formulation of enteric-coated peppermint that provides sustained release to the small intestine and, potentially, fewer adverse effects.

Methods: A comprehensive literature search identified published randomized, placebo-controlled trials of peppermint oil in adult patients with IBS. Treatment duration was required to be ≥2 weeks, and follow-up ranged from 3 to 12 weeks. The primary outcomes were global improvement in IBS symptoms and improvement in IBS-related abdominal pain.

Results: The analysis included 12 studies with a total of 835 patients. Global improvement in IBS symptoms was evaluated in 7 studies. The risk ratio* for global improvement with peppermint oil versus placebo was 2.35 (p<0.00001), with a number needed to treat* of 3. Improvement in abdominal pain—reported in 6 studies—had a risk ratio of 1.78 with peppermint oil vs placebo (p<0.00001) and a number needed to treat of 4. The studies reported similar frequencies of adverse events in peppermint oil and placebo groups. The most commonly reported were heartburn, dry mouth, belching, peppermint taste, rash, dizziness, and headache; most were mild and transient.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis; however, the source of funding was not included.

Alammar N, et al: The impact of peppermint oil on the irritable bowel syndrome: a meta-analysis of the pooled clinical data. *BMC Complementary and Alternative Medicine* 2019; doi 10.1186/s12906-18-2409-0. From Johns Hopkins University School of Medicine, Baltimore, MD; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

*See Reference Guide.

Early Levodopa in Parkinson's

According to the results of a randomized delayed-start trial, early initiation of levodopa (plus carbidopa; *Sinemet*) does not slow disease progression in Parkinson's disease.[1] The study results support current practice: treatment that is guided by clinical need.

Background: The possibility that levodopa might modify the course of Parkinson's disease was suggested by the previously published Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) study.[2] The present study was designed to replicate many of the features of the ELLDOPA trial, including drug dosage, duration of double-blind treatment, and primary outcome.

Methods: The trial enrolled patients from community and academic hospitals in the Netherlands. Patients had received a diagnosis of Parkinson's disease within the previous 2 years, had taken no antiparkinsonian medication, and were not candidates for immediate symptom relief with levodopa. At baseline, patients were randomly assigned to active treatment with 100 mg levodopa plus 25 mg carbidopa t.i.d. or to placebo. After 40 weeks, all patients received active medication for

an additional 40 weeks. Patients in either group who developed a disability requiring medication during the double-blind phase were switched to open-label levodopa–carbidopa. The primary study outcome was change from baseline to week 80 in the Unified Parkinson's Disease Rating Scale (UPDRS). Based on the ELLDOPA trial, the investigators expected to find a between-group difference of 4 points on the 176-point UPDRS, a difference that has been considered clinically relevant.

Results: A total of 445 patients participated in the trial, of whom 417 completed the 80th week. Study participants had a mean age of 65 years and a mean baseline score of 28–29 on the UPDRS. A total of 87 patients in the delayed-start (placebo) group and 24 in the early-start group developed symptoms requiring unblinding and a switch to open-label medication.

After 80 weeks, UPDRS scores did not differ between the early-start and delayed-start groups. Patients in the early-start group improved by a mean of 1 point, and the delayed-start group improved by 2 points, a nonsignificant difference. The early-start group had a larger symptomatic improvement by week 40, but this difference was no longer apparent after both groups received active medication. Secondary outcomes, including symptom progression, disability, cognitive function, depression, and quality of life, also did not differ between the 2 groups at week 80. During randomized treatment, the incidence of nausea was higher in the early-start group (23% vs 14%), but other adverse effects did not differ between the groups.

Discussion: The present results clarify the ambiguous results of the ELLDOPA trial, and suggest that levodopa treatment does not have a disease modifying effect in Parkinson's disease

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

[1]Verschuur C, et al: Randomized delayed-start trial of levodopa in Parkinson's disease. *NEJM* 2019;380 (January 24):315–324. doi 10.1056/NEJMoa1809983. From the University of Amsterdam, the Netherlands; and other institutions. **Funded by the Netherlands Organization for Health Research and Development; and other sources. Four of 12 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**
[2]Fahn S, et al. Levodopa and the progression of Parkinson's disease. *NEJM* 2004;351:2498–2508.

*See Reference Guide.

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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.

Network Meta-Analysis: A study design that can provide estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common.

Number Needed to Treat (NNT): Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Risk Ratio: 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.

Standardized Mean Difference: The difference between two normalized means used for comparison of data obtained using different scales, a value of 0 to 0.2 is considered a negligible effect, 0.2 to 0.5 a small effect, 0.5 to 0.8 a medium effect, and >0.8 a large effect.

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.