

New and Emerging Pharmacologic Therapies for Type 2 Diabetes, Dyslipidemia, and Obesity

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ABSTRACT

Background: Type 2 diabetes, dyslipidemia, and obesity continue to be common disorders that many clinicians and patients struggle to control. There are likely numerous reasons for poor control of these diseases, including medication efficacy and adverse effects, access to medications and health care, poor adherence, and lack of lifestyle changes by patients. Several new and emerging medications may help resolve these issues.

Objective: The goal of this article is to review new and emerging medications for type 2 diabetes mellitus, dyslipidemia, and obesity.

Methods: The Food and Drug Administration drug approval list for 2011 and 2012 was searched to identify newly approved drugs for type 2 diabetes, dyslipidemia, and obesity. New drug entities or existing drug entities with a new indication were included. To identify emerging therapies, we performed targeted searches on clinicaltrials.gov using the listed disease states and Phase III studies. PubMed was searched with these drug names to identify clinical trials for inclusion in this review. Preclinical trials and non-English-language publications were excluded, as were trials not evaluating the efficacy of these agents. The websites goodRx.com and rxpriceverif.com were used to identify pricing.

Results: For type 2 diabetes, exenatide extended-release causes fewer adverse effects and better efficacy than the daily exenatide formulation. The new sodium-glucose cotransporter 2 inhibitor drug class has a unique mechanism of action, hemoglobin A_{1c} reductions near 1%, and seemingly few adverse effects. With respect to dyslipidemia, icosapent ethyl effectively lowers triglyceride levels by ~20% to 45% (depending on baseline triglyceride level), with little effect on LDL-C. For treatment of obesity, lorcaserin is a novel anorexic agent that results in an ~5.5-kg mean weight loss, and

phentermine-topiramate controlled-release reduces weight by ~12.2 kg.

Conclusion: Although these agents certainly add to our armamentarium, none appear to offer significant advantages over currently available options. High costs will likely prevent these novel agents from being used as first-line agents in most patients. Further studies will help to more clearly define their roles in therapy. (*Clin Ther.* 2013;35:A3-A17) © 2013 Elsevier HS Journals, Inc. Elsevier HS Journals, Inc. All rights reserved.

Key words: obesity, diabetes, dyslipidemia, exenatide extended-release, dapagliflozin, canagliflozin, Icosapent ethyl.

INTRODUCTION

Type 2 diabetes, dyslipidemia, and obesity continue to be common disorders that many clinicians and patients struggle to control. Type 2 diabetes affects nearly 26 million people in the United States, or >8% of the overall population, and 27% of those older than 65 years.¹ Furthermore, only ~50% to 60% of those with type 2 diabetes have achieved their glycemic goals.¹ Approximately 71 million Americans, or more than one-third of the population, have high cholesterol levels. Of these, only approximately one-third have achieved the cholesterol goals.¹ Obesity also affects approximately one-third of the population.¹ All of these individuals are at an increased risk for a multitude of complications. There are likely numerous reasons for poor control of these diseases, including medication efficacy and adverse effects, access to medications and health care, poor adherence, and lack of

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Table I. New and Emerging Pharmacologic Therapies for Type 2 Diabetes, Dyslipidemia, and Obesity.

| Drug | Indication | Dosing | Adverse Effects |
|----------------------------|-----------------------------|---|---|
| Exenatide extended-release | Adults with type 2 diabetes | 2 mg SQ once weekly | Nausea, vomiting, diarrhea |
| Dapagliflozin | Type 2 diabetes | Unknown* | Possible increased risk UTIs |
| Canagliflozin | Type 2 diabetes | Unknown* | Possible increased risk UTIs |
| Icosapent ethyl | Hypertriglyceridemia | 2 g twice daily | Diarrhea, nausea, arthralgia |
| Lorcaserin | Obesity | 10 mg twice daily | Arthralgia, headache, URT symptoms, dizziness, nausea, constipation, fatigue, dry mouth |
| Phentermine-topiramate CR | Obesity | 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, 15 mg/92 mg once daily | Paraesthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth |

CR = controlled release; SQ = subcutaneous; URT = upper respiratory tract; UTI = urinary tract infection.

*Currently in Phase III development.

lifestyle changes by patients. There are several new and emerging medications that may help resolve some of these issues (Table I). In this review, we discuss these medications, including their efficacy, adverse effects, potential role in therapy, and cost issues.

METHODS

The Food and Drug Administration (FDA) drug approval list for 2011 and 2012 was searched to identify newly approved drugs for type 2 diabetes, dyslipidemia, and obesity.² New drug entities or existing drug entities with a new indication were included. To identify emerging therapies, targeted searches on clinicaltrials.gov were completed using the listed disease states and Phase III studies. PubMed was then searched using the drug names (exenatide extended-release, dapagliflozin, canagliflozin, icosapent ethyl, lorcaserin, phentermine, and topiramate) to identify clinical trials for inclusion in this review. Preclinical trials and non-English-language publications were excluded, as were trials not focusing on evaluating the efficacy of these agents as their primary outcome. Only fully published, original research articles were included. The PubMed search for exenatide once weekly yielded 5 trials that met our criteria. There were 6 results for dapagliflozin and 1 for canagliflozin that met our criteria. For dyslipidemia, 3 trials were identified. For obe-

sity, a total of 6 articles were identified: 3 with lorcaserin and 3 with the combination of phentermine-topiramate controlled-release (phen-top CR). The website rxpriceverify.com was used to obtain most pricing information. The website goodRx.com was used to identify pricing when other references were not available.

RESULTS

We identified 5 efficacy trials involving exenatide extended-release and 3 trials studying various sodium-glucose cotransporter 2 (SGLT2) inhibitors for the treatment of type 2 diabetes.

With respect to dyslipidemia, we identified 2 efficacy trials involving icosapent ethyl. Three trials for lorcaserin and 3 for phentermine plus topiramate were identified for obesity.

Type 2 Diabetes

Exenatide Extended-Release

Exenatide BID* reached the US market in 2005 as the first glucagon-like peptide 1 (GLP-1) agonist.³ This incretin mimetic increases GLP-1, which is reduced in people with type 2 diabetes.³ This results in an increase in glucose-dependent insulin secretion by

*Byetta™ (Amylin Pharmaceuticals, Inc, San Diego, California).

the pancreatic β cell, suppression of inappropriately elevated glucagon secretion, and slowed gastric emptying.³ Increased satiety and sustained weight loss are also seen with exenatide.³ These medications have also been reported to reduce the loss of β cells over time.³ One major drawback to exenatide is the very high incidence of nausea and vomiting.³ It was hoped that an extended-release formulation would provide the same benefits but reduce the gastrointestinal adverse effects.

Exenatide extended-release[†] was released in the United States in January 2012. It is a once weekly subcutaneous injection indicated for type 2 diabetes. The dose is 2 mg once weekly (every 7 days) at any time of day without regard to meals. In case a patient misses a regularly scheduled dose, the missed dose may be administered as long as the next regularly scheduled dose is not due within 3 days. Exenatide extended-release is not recommended as first-line therapy for drug-naïve patients whose diabetes is not controlled with diet and exercise. It also has not been studied for use in combination with insulin.

The tolerability and efficacy of exenatide extended-release were studied in the DURATION (Diabetes Therapy Utilization: Researching Changes in A_{1c}, Weight and Other Factors Through Intervention with Exenatide Once Weekly) trials. DURATION-1 compared effects of exenatide 2 mg once weekly to exenatide BID (5 μ g BID titrated to 10 μ g BID after 28 days) in 259 patients for 30 weeks.⁴ Participants in both groups had similar baseline characteristics; the mean baseline level of glycosylated hemoglobin A_{1c} (HbA_{1c}) in both groups was 8.3%. After 30 weeks the exenatide once weekly group had a mean HbA_{1c} reduction of 1.9% compared with 1.5% in the exenatide BID group ($P = 0.002$). Nausea occurred in 26.4% patients of the once weekly group compared with 34.5% of the BID group. Vomiting was also more frequent in the BID group (18.6% vs 10.8%). Total cholesterol level, triglycerides level, and blood pressure improved in both groups.

DURATION-2 compared the addition of exenatide once weekly, sitagliptin, or pioglitazone to existing metformin therapy in 491 patients.⁵ Mean baseline HbA_{1c} among participants in the 3 groups was 8.5%, and they were followed up for 26 weeks after randomization. At the end of the study, HbA_{1c} reductions were

as follows: -1.5% (95% CI, -1.7% to -1.4%) for the exenatide group, -0.9% (95% CI, -1.1% to -0.7%) for the sitagliptin group, and -1.2% (95% CI, -1.4% to -1.0%) for pioglitazone group. The HbA_{1c} reduction with exenatide once weekly was statistically significant compared with sitagliptin ($P < 0.001$) and pioglitazone ($P = 0.02$). Nausea (24% of exenatide patients), diarrhea (18% of exenatide patients), and vomiting (11% of exenatide patients) rates were much higher in the exenatide group.

The next study, DURATION-3, randomized 456 patients with uncontrolled type 2 diabetes to exenatide 2 mg once weekly or insulin glargine (starting dose of 10 units and titrated to a glucose of 72 to 99 mg/dL).⁶ Seventy percent of the patients were using metformin before randomization, and the remainder were using metformin with a sulfonylurea. After 26 weeks, the level of HbA_{1c} decrease was significantly better in the exenatide group (-1.5% vs -1.3% , $P = 0.01$).

DURATION-4 assessed the efficacy of exenatide once weekly compared with metformin, pioglitazone, and sitagliptin among drug-naïve patients with type 2 diabetes.⁷ A total of 820 patients were randomized to receive exenatide extended-release 2 mg once weekly, metformin 2000 mg/d, pioglitazone 45 mg/d, or sitagliptin 100 mg/d for 26 weeks. The mean baseline HbA_{1c} was 8.5% for all groups; all other baseline characteristics were comparable. Participants had been diagnosed as having type 2 diabetes for a mean of 2.7 years before enrollment. After 26 weeks, mean HbA_{1c} reductions for exenatide vs metformin, pioglitazone, and sitagliptin were -1.53% vs -1.48% ($P = .62$), -1.63% ($P = .33$), and -1.15% ($P < 0.001$), respectively. Weight changes with exenatide were comparable to those with metformin and better than those with pioglitazone and sitagliptin. Nausea and diarrhea was reported in 11.3% and 10.9% of exenatide patients, respectively.

DURATION-5 was similar to DURATION-1 and compared exenatide 2 mg once weekly to exenatide 5 μ g BID titrated to 10 μ g BID after 28 days in 252 patients during 24 weeks.⁸ After 24 weeks, the mean HbA_{1c} decreased by 1.6% in the once weekly group compared with a decrease of 1.0% in the BID group ($P < 0.001$). Similarly, fasting glucose reductions were -35 mg/dL versus -12 mg/dL ($P < 0.001$).

On the basis of the DURATION trials, exenatide extended-release is more efficacious than exenatide BID with fewer gastrointestinal side effects. Exenatide extended-release also appears to be more efficacious

[†]Bydureon™ (Amylin Pharmaceuticals, Inc, San Diego, California).

than sitagliptin and basal insulin but is associated with more gastrointestinal adverse effects than these agents. Its efficacy is comparable to metformin and pioglitazone.

SGLT2 Inhibitors

The next novel class of agents for type 2 diabetes to reach the US market will likely be the SGLT2 inhibitors. These drugs reduce the reabsorption of glucose through inhibition of SGLT2 of the renal SGLT glucose transporter family, which is responsible for mediating ~90% of renal glucose reabsorption in the S1 segment of the proximal convoluted tubule. SGLT1 accounts for the other 10%. Thus, inhibition of SGLT2 will inhibit most renal glucose reabsorption, resulting in glucosuria. Additional advantages of this class of agents are that they do not require functioning β cells to be effective and do not cause hypoglycemia.

There are 6 SGLT2 inhibitors in Phase III of development (dapagliflozin, canagliflozin, empagliflozin, ibragliflozin, luseogliflozin, and topogliflozin) and several others in earlier stages of development. Dapagliflozin has the most published clinical trials to date. Ferrannini et al⁹ studied dapagliflozin in 474 treatment-naïve patients with type 2 diabetes. There were several parallel groups in the study who received 2.5, 5, or 10 mg daily of dapagliflozin or placebo. In one group, dapagliflozin decreased HbA_{1c} by 0.58% to 0.89%. However, in those who had high baseline HbA_{1c} levels (10%-12%), HbA_{1c} was reduced by 2.66% to 2.88%. Nauck et al¹⁰ compared the addition of dapagliflozin or glipizide to metformin in ~800 patients with uncontrolled diabetes. HbA_{1c} decreased by a mean of 0.52% in both groups after 1 year of treatment. During this time, weight decreased by 3.22 kg in the dapagliflozin group and increased by 1.44 kg in the glipizide group. Bailey et al¹¹ evaluated the addition of placebo versus various doses of dapagliflozin (2.5-10 mg/d) to metformin in 534 patients. After 24 weeks, the mean HbA_{1c} level decreased 0.3% in the placebo group, 0.67% in the dapagliflozin 2.5 mg group ($P < 0.001$), 0.7% in the dapagliflozin 5 mg group ($P < 0.001$), and 0.84% in the dapagliflozin 10 mg group ($P < 0.001$). Lastly, Strojek et al¹² randomly assigned 597 patients with uncontrolled diabetes taking glimepiride to the addition of placebo or dapagliflozin 2.5, 5, or 10 mg. After 24 weeks, the HbA_{1c} level decreased by 0.13%, 0.58%, 0.63%, and 0.82%, respec-

tively (all $P < 0.0001$ vs placebo). Rosenstock et al¹³ randomized 360 patients with type 2 diabetes who were taking pioglitazone to the addition of dapagliflozin 5 mg or 10 mg or placebo. After 24 weeks, the HbA_{1c} level decreased by 0.42% in those who received placebo, 0.82% in those who received dapagliflozin 5 mg, and 0.97% in those who received dapagliflozin 10 mg ($P < 0.001$). Lastly, Wilding et al¹⁴ evaluated the efficacy of adding dapagliflozin to existing insulin therapy (with or without oral therapy) in 808 patients with type 2 diabetes. After 24 weeks, the HbA_{1c} level decreased by 0.79% to 0.96% with the addition of dapagliflozin (depending on dose) and by 0.39% with placebo ($P < 0.001$).

Similar results in HbA_{1c} reduction have been seen with canagliflozin. Rosenstock et al¹⁵ evaluated 5 different doses of canagliflozin in 451 patients with uncontrolled diabetes who were taking metformin alone. After 12 weeks, the HbA_{1c} level decreased by a mean of 0.70% to 0.95% with the addition of canagliflozin. Doses of 300 mg once daily (QD) or BID produced HbA_{1c} reductions at the higher end of that range. Weight also decreased significantly in the canagliflozin group compared with placebo or sitagliptin. There was also evidence of β cell function improvement with canagliflozin.

The SGLT2 inhibitors appear to be generally well tolerated. Urinary tract infections occurred more often in some studies in patients taking an SGLT2 inhibitor compared with those taking a sulfonylurea or placebo. A range of 4.2% to 8.8% of patients receiving dapagliflozin experienced signs and symptoms of urinary tract infections (risk increases in a dose-dependent manner) compared with 6.4% of patients taking placebo or glipizide.⁸ It is possible that the increased glucosuria caused by SGLT2 inhibitors provides a medium for better bacterial growth. No difference was found between the 2 groups in the number of diagnosed urinary tract infections. Adverse renal effects are also of potential concern based on the mechanism of action of these drugs, but short-term data do not suggest any adverse renal effects to date. A small potential risk for developing bladder or breast cancer emerged in some of the trials.^{9-14,16} To date, there have been nearly 4500 patients subjected to at least one dose of dapagliflozin for a total of nearly 1900 patient-years. Of these, there have been 7 cases of bladder cancer in dapagliflozin-treated patients and none in the control groups. Breast cancer was detected in 9 of 4287 (0.2%) patients in the dapagliflozin group versus 0 of 1941 control group

patients.¹⁶ In January 2012, the FDA requested additional clinical trial data to clarify any possible risk for bladder or breast cancer. This information will be reviewed before any of these drugs reach the market.

It is too early to tell if there are any clinically significant differences among the individual SGLT2 inhibitors. Numerous Phase III trials investigating SGLT2 inhibitors are ongoing at this time. In addition to the beneficial effects of SGLT2 inhibitors on weight and HbA_{1c}, reductions in systolic blood pressure (up to 5 mm Hg) have been reported in some trials and are believed to be related to the chronic osmotic diuresis caused by the glycosuria.¹⁶ There does not appear to be any effect on lipids.¹⁶ Importantly, data on major vascular outcomes are limited at this point.¹⁶

The American Diabetes Association and European Association for the Study of Diabetes updated their consensus algorithm in 2012.¹⁷ Cost was included as one of several key attributes for the various treatment options. Metformin is typically considered to be first-line therapy for type 2 diabetes because it is highly effective, has a low risk of hypoglycemia, and is rather inexpensive. Many options exist as add-on therapy to metformin, including thiazolidinediones, sulfonylureas, dipeptidyl peptidase IV inhibitors, GLP-1 agonists, insulin, and, eventually, the SGLT2 inhibitors. These new agents will likely be cost prohibitive for the uninsured. When cost is a driving force in drug selection, sulfonylureas would be the best second-line agent. Sulfonylureas have some disadvantages, such as hypoglycemia and weight gain, but none of the second-line agents are devoid of potential disadvantages. Sulfonylureas can be highly effective and are very appropriate second-line agents. Another potential option would be adding basal insulin. Several options exist here, and although they are more expensive than sulfonylureas, they are more effective and cheaper than all the newer agents. Regardless, when selecting an agent, numerous factors need to be considered, including efficacy, adverse effects, cost, and expected patient adherence. Obviously, cost can affect adherence but so can route of administration, and some patients may not be willing to inject themselves or take medication 3 or 4 times a day.

Dyslipidemia

Icosapent ethyl[‡] was approved by the FDA on July 26, 2012, with the indication for the treatment of hypertriglyceridemia, specifically with triglyceride levels

≥500 mg/dL. This medication, manufactured by Amain Pharma Inc, is currently being produced as a 1-g oral capsule.¹⁸ The recommended dose is 4 g/d given as 2 g BID. Icosapent ethyl (AMR101) is a novel lipid-altering agent that contains ≥96% eicosapentaenoic acid ethyl ester and essentially no docosahexaenoic acid.¹⁹ This distinction is important when comparing other ω3 products currently on the market. Some data suggest that the products on the market increase LDL-C due to the docosahexaenoic acid component and that the elimination of docosahexaenoic acid would reduce this unwanted effect.¹⁹

The proposed mechanisms of action of icosapent ethyl include the reduction of hepatic VLDL triglycerides synthesis and/or secretion and the enhancement of triglyceride clearance from circulating VLDL particles. Other proposed mechanisms of action include increased β-oxidation, inhibition of acyl-coenzyme A:1,2-diacylglycerol acyltransferase, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity.¹⁸

In 2011, Bays et al¹⁹ published an article entitled “Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Patients With Very High Triglyceride Levels (from the Multi-center, placebo-controlled, Randomized, double-blIND, 12-week study with an open-label Extension [MARINE] Trial).” Participants were divided onto 3 treatment groups: icosapent ethyl 4 g/d (n=77) (dosed as two 1-g capsules taken BID), or icosapent ethyl 2 g/d (n=76) (dosed as one 1-g capsule BID), or placebo (n=76). Participants were enrolled if their triglyceride levels were ≥500 mg/dL but ≤2000 mg/dL unless they met one of the many exclusion criteria. Some of these criteria included history of pancreatitis, body mass index (BMI) ≥45 kg/m², HbA_{1c} ≥9.5%, history of stroke or myocardial infarction, and creatine kinase elevation owing to known muscle disease. Participant demographic characteristics, including a mean age of 52.9 years, mean BMI of 30.8 kg/m², statin use among 25%, and 28% having a diagnosis of type 2 diabetes, were similar among all 3 groups. However, 88% of the patients were white and 76% were male. The median baseline triglyceride level was 679.5 mg/dL, with 35% of the patients having levels >750 mg/dL.¹⁹

Before drug therapy was initiated, patients in the MARINE trial first entered a 4-week stabilization period of diet and exercise, which could be extended based on previous lipid therapy. Patients were only

[‡]Vascepa™ (Amain Pharma, Inc, Bedminster, New Jersey).

allowed to continue statin therapy if deemed at a high risk for coronary heart disease. All other patients taking a statin, fibrate, niacin, and/or ω 3 fish oil therapy stopped taking medication at the initiation of the stabilization period.¹⁹

After 12 weeks of treatment in the MARINE trial, triglyceride levels were reduced by 33.1% ($P < 0.001$) and 19.7% ($P = 0.005$) in the 4-g/d and 2-g/d treatment groups, respectively, when compared with placebo. For patients specifically with triglyceride levels >750 mg/dL, triglyceride levels were lowered by 45.4% ($P = 0.0001$) in the 4-g/d treatment group.¹⁹ Importantly, no significant difference were found in LDL levels between the treatment groups. Adverse events reported included diarrhea, nausea, and eructation. However, no significant difference was found in adverse drug events (ADEs) or metabolic adverse effects, including HbA_{1c} and fasting blood glucose levels, between treatment groups.¹⁹

Ballantyne et al²⁰ published an article entitled “Efficacy and Safety of Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Statin-Treated Patients With Persistent High Triglycerides (from the ANCHOR Study).” The study aim was to assess the efficacy and tolerability of icosapent ethyl in statin-treated patients at high cardiovascular risk with well-controlled LDL-C and residually high triglyceride levels (≥ 200 and ≤ 500 mg/dL). This Phase III, multicenter, placebo-controlled, randomized, double-blinded, 12-week clinical trial included 702 patients who were ≥ 18 years of age and at high risk for cardiovascular disease (CVD), as defined by the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines.²¹ These participants had to have been willing to maintain a stable diet and exercise regimen throughout the study. Other exclusion criteria included HbA_{1c} level $\geq 9.5\%$, BMI >45 kg/m², non-HDL-C level <100 mg/dL, long-term treatment with antihypertensive and/or antidiabetic medications, or increased creatine kinase from known muscle disease.²⁰

Patients in the ANCHOR trial were randomized to receive icosapent ethyl 4 g/d, icosapent ethyl 2 g/d, or placebo.²⁰ At the end of the 12-week trial, icosapent ethyl 4 g/d statistically significantly reduced triglyceride levels by 28.4% ($P < 0.001$), 18.8% ($P < 0.001$), and 23.4% ($P < 0.001$) in patients treated with atorvastatin, simvastatin, and rosuvastatin, respectively. A decrease in triglyceride levels of 14.3% ($P < 0.001$)

was also seen in the 2-g/d group in patients treated with simvastatin. When comparing results among patients with type 2 diabetes to patients without diabetes, triglyceride levels were reduced by 32.2% ($P < 0.001$) and 9.8% ($P = 0.007$) in the 4-g/d and 2-g/d groups, respectively, among people with diabetes. The nondiabetes group experienced a decrease in triglyceride levels of 16.8% ($P < 0.001$) and 10.8% ($P = 0.03$) in the 4-g/d and 2-g/d groups, respectively.²⁰

Within the 12-week study period, 46.4% of the patients of patients in the ANCHOR study reported an ADE.²⁰ Gastrointestinal events (13.4% total), infections and infestations (14.1% total), and musculoskeletal and connective tissue disorders (6.6% total) were found to be no different between groups. Of these ADEs, diarrhea (3.4%, 3.8%, and 4.3%), nausea (2.1%, 2.1%, and 3.0%), nasopharyngitis (0.4%, 2.5%, and 3.0%), and arthralgia (1.7%, 3.4%, and 0.4%) were the highest reported ADE in the 4-g/d, 2-g/d, and placebo groups, respectively. Arthralgia was the only ADE occurring at a higher percentage in the icosapent ethyl groups versus the placebo group; however, this result was not reported to be statistically significant. This study reports that icosapent ethyl did not significantly increase LDL-C at either dose. No statistically significant increases in fasting plasma glucose or hemoglobin HbA_{1c} were observed in either treatment group compared with the placebo group.²⁰

Other current treatments for hypertriglyceridemia include fibrates, niacin, and other forms of fish oil, which include both docosahexaenoic acid and eicosapentaenoic acid. Fibrates significantly reduce the triglyceride levels in patients with very high triglyceride levels but can also substantially increase the LDL-C levels by as much as 45%.²² Fish oils rich in eicosapentaenoic acid and docosahexaenoic acid report significant reduction in triglyceride levels of 26% to 47% but with an increase in LDL-C levels of 17% to 46% in those with hypertriglyceridemia.²³ When comparing these treatments to the data found in both the MARINE and ANCHOR trials, icosapent ethyl appears to have the same efficacy on lowering triglyceride but with no significant effect on LDL-C values.

Pricing information is not yet available for icosapent ethyl and will likely be determined once the FDA rules on the length of market exclusivity this product. In comparison, prices for a 1-month supply (www.rxpriceverify.com), at varying strengths, for the competitor medications are as follows: fenofibrate 145 mg,

\$135; gemfibrozil 600 mg, \$15.00; ω 3-acid ethyl esters 1 g, \$184.00; and niacin 1 g, \$156.60.

Use of icosapent ethyl is cautioned in those with hypersensitivity to fish and/or shellfish and in patients at an increased risk of bleeding. In addition, arthralgia was the only ADE that seemed to increase with the use of this medication.²⁰ Icosapent ethyl does not currently require any routine monitoring other than as indicated for cholesterol management. In patients with hepatic impairment, aspartate aminotransferase and alanine aminotransferase levels should be monitored periodically.

Both the ATP III and American Association of Clinical Endocrinologist, along with other clinical guidelines, such as the Cardiometabolic Risk Consensus statement from the American Diabetes Association and the American College of Cardiology Foundation and “Managing Abnormal Blood Lipids: A Collaborative Approach,” recommend the treatment of LDL-C cholesterol first in patients with hyperlipidemia and/or dyslipidemia.^{21,24–26} These guidelines also acknowledge the use of statin therapy as first-line treatment. For patients with triglyceride levels between 200 and 499 mg/dL, the ATP III guidelines recommend niacin therapy; however, for those with triglyceride levels \geq 500 mg/dL fibrates are first choice. The guidelines further state that either can be used, depending on how the patient tolerates therapy. The use of icosapent ethyl is currently limited, and the need for further trials to determine its true benefit and place in therapy are needed. Currently, the REDUCE-IT trial (Reduction of Cardiovascular Events with EPA – Intervention Trial), “a study of AMR101 to evaluate its ability to reduce cardiovascular events in high risk patients with hypertriglyceridemia and on a statin,” is recruiting patients.²⁷ This study will help determine where icosapent ethyl fits into the treatment of dyslipidemia.

Obesity

Lorcaserin

Lorcaserin is a novel agent that acts as an agonist at central serotonin subtype 2c (5-HT_{2C}) receptors on hypothalamic pro-opiomelanocortin neurons, although the exact mechanism is not fully understood.²⁸ The weight loss effects of lorcaserin are believed to be due to agonism of central 5-HT_{2C} receptors, leading to reduced caloric intake and increased satiety.^{29–32} Lorcaserin is selective for the 5-HT_{2C} subtype and does not have significant activity at either 5-HT_{2B} or 5-HT_{2A} receptors; activity at the 5-HT_{2B} receptor has been as-

sociated with the development of valvular heart disease, leading to the removal of previous antiobesity agents such as dexfenfluramine.^{28,32}

The tolerability and efficacy of lorcaserin for the treatment of obesity have been evaluated in 3 large randomized, placebo-controlled, double-blind studies, which provided the basis for FDA approval in June 27, 2012. The BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management) trial included patients who were 18 to 65 years of age with a BMI of 30 to 45 kg/m² or those with a BMI of 27 to 29.9 kg/m² with at least one concomitant weight-related comorbidity such as hypertension, dyslipidemia, CVD, impaired glucose tolerance, or obstructive sleep apnea.²⁹ A total of 4008 participants were randomized to receive either lorcaserin 10 mg QD (n=801), lorcaserin 10 mg BID (n=1602), or placebo (n=1601) for 52 weeks in addition nutritional and exercise counseling provided at each study visit. The mean baseline weight and BMI were 100 kg and 36 kg/m², respectively.²⁹ The primary outcome was the proportion of participants who lost at least 5% or 10% of baseline weight. Analyses included a modified intention-to-treat (mITT) approach with the last observation carried forward (LOCF). After 1 year of treatment 47.2% of those receiving lorcaserin BID lost >5% of their baseline weight compared with 40.2% of those receiving lorcaserin QD and 25% of those receiving placebo ($P < 0.001$ for both doses of lorcaserin vs placebo). Greater than 10% weight loss was achieved by 22.6% receiving lorcaserin BID, 17.4% receiving lorcaserin QD, and 9.7% receiving placebo ($P < 0.001$ for both doses vs placebo). Absolute weight loss, calculated by least squares mean, was 5.8 kg, 4.7 kg, and 2.9 kg for lorcaserin BID, lorcaserin QD, and placebo, respectively.²⁶ Although systolic blood pressure, diastolic blood pressure, and heart rate decreased in all groups, the difference was not statistically significantly different. Importantly, no differences were noted between lorcaserin and placebo in echocardiographic outcomes.²⁹

The second study investigating lorcaserin, the BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) study, enrolled people 18 to 65 years of age with a baseline BMI of 30 to 45 kg/m² or a BMI of 27 to 45 kg/m² with at least one concomitant weight-related comorbidity, such as hypertension, CVD, dyslipidemia, impaired glucose tolerance, or obstructive sleep apnea.³⁰ A total of 3182 participants were randomized to receive lorcaserin 10 mg BID (n=1595) or placebo (n=1587) for 52 weeks.

At 52 weeks those receiving placebo continued for an additional 52 weeks, whereas those receiving lorcaserin BID were randomized in a 2:1 ratio to continue receiving lorcaserin or be switched to placebo. A total of 573 participants received lorcaserin for 2 years, 283 received lorcaserin for 1 year and placebo for 1 year, and 697 received placebo for 2 years; nutritional and exercise counseling was provided at each visit. At randomization the mean weight and BMI was 100 kg and 36 kg/m², respectively.³⁰ The primary outcome, percentage of patients who achieved >5% weight loss of baseline weight after 52 weeks, occurred in 47.5% of those receiving lorcaserin compared with 20.3% receiving placebo (mITT population with LOCF, $P < 0.001$). The mean decrease in weight (calculated using the least squares mean) was 5.8% (5.8 kg) for lorcaserin compared with 2.2% (2.2 kg) for placebo. After 104 weeks of treatment more patients who continued taking lorcaserin were able to maintain weight loss of >5% compared with those who transitioned to placebo (67.9% vs 50.3%, $P < 0.001$). Secondary outcomes, including percentage achieving >10% weight loss ($P < 0.001$), reduction in waist circumference, blood pressure reduction, and BMI, were improved with lorcaserin after 52 weeks of treatment, although the clinical significance of these differences may be questionable. There was no difference between groups in FDA-defined valvulopathy, but due to a low rate of occurrence in both groups the study only had 60% power to rule out a relative risk ratio of 1.5 for lorcaserin compared with placebo.²⁷

The third study (BLOOM-DM [(Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus]) enrolled people aged 18 to 65 years with a BMI of 27 to 45 kg/m² and a diagnosis of type 2 diabetes with an HbA_{1c} level of 7% to 10%. Before randomization, participants could only have received metformin, a sulfonylurea, or both for the treatment of their type 2 diabetes.³¹ Patients were stratified based on baseline type 2 diabetes treatment and randomized to lorcaserin 10 mg BID (n=256), lorcaserin 10 mg QD (n=95), or placebo (n=253) for 52 weeks; enrollment into the lorcaserin 10 mg QD group was stopped after 8 months because of slow enrollment. Patients received standardized nutritional and exercise counseling at each visit. At baseline the mean baseline weight was 104 kg, and the mean baseline BMI was 36 kg/m².³¹

The primary outcome of the BLOOM-DM study was the proportion of patients losing at least 5% and 10% of baseline weight after 52 weeks of treatment; results were analyzed in the mITT population with the LOCF. Approximately 45% and 38% of the lorcaserin QD and BID patients, respectively, achieved at least 5% weight loss compared with only 16% in the placebo group ($P < 0.001$ for both doses compared with placebo). A >10% reduction in weight was achieved by only 4.4% in the placebo group compared with 16.3% of those receiving lorcaserin BID and 18.1% of those receiving lorcaserin QD ($P < 0.001$ for both doses compared with placebo). Absolute weight loss (using least squares means) was 4.7 kg for lorcaserin BID, 5 kg for lorcaserin QD, and 1.6 kg for placebo. Treatment with lorcaserin also improved secondary outcomes, although the absolute changes in many of the secondary outcomes were minor and are of unknown clinical relevance. Incidence of FDA-defined valvular disease did not differ between groups.³¹

On the basis of the results of these studies,^{29–31} lorcaserin is approved at a dose of 10 mg BID in patients with a BMI of >30 kg/m² or a BMI of >27 kg/m² with at least one weight-related comorbidity, such as hypertension, type 2 diabetes, or dyslipidemia, in addition to a reduced calorie diet and increased physical activity. The labeling indicates response to therapy should be assessed at week 12 and if there is a <5% decrease in weight use of the drug should be discontinued because it will be unlikely that the patient will achieve and sustain adequate weight loss with continued treatment. The most common adverse events with lorcaserin include headache, upper respiratory tract symptoms and infection, dizziness, nausea, constipation, fatigue, and dry mouth. Lorcaserin is estimated to cost approximately \$4 per day.³³

Phen-Top CR

Exenatide BID[§] in combination with topiramate controlled-release was FDA approved on July 17, 2012, based on tolerability and efficacy data from 3 large randomized, double-blind, placebo-controlled trials. The anorexic effects of phentermine are believed to be due to its action as a sympathomimetic amine in causing the release of catecholamines in the hypothalamus, which is theorized to reduce appetite and decrease food consumption. The mechanism re-

[§]Qsymia (VIVUS Inc, Mountain View, California).

sponsible for topiramate's anorexic effects is unknown, but it appears to promote satiety and appetite suppression and may be due to effects on neurotransmitters, neurotransmission, or inhibition of carbonic anhydrase.³⁴ Phen-top CR provides different mechanisms of action for weight loss, while using lower doses than would be used for monotherapy, to minimize adverse effects.

The EQUIP trial (Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized

Controlled Trial) included people aged 18 to 70 years with a BMI of $>35 \text{ kg/m}^2$ with no upper limit, a fasting blood glucose level $<100 \text{ mg/dL}$, and a blood pressure $<140/90 \text{ mmHg}$ while receiving 0 to 2 medications.³⁵ Participants were stratified by sex and randomized to phen-top CR 15 mg/92 mg ($n=512$), phen-top CR 3.75 mg/23 mg ($n=241$), or placebo ($n=514$) for 52 weeks. Phen-top CR was started at 3.75 mg/23 mg and titrated at weekly intervals by 3.75 mg/23 mg to the target dose. All participants received standard-

Table II. Diabetes Clinical Trials Summary.

| Drug | Design and Intervention | Results | P | Reference |
|----------------------------|--|---|--|-----------|
| Exenatide extended-release | RCT, exe 2 mg once weekly vs exe 10 μg BID ($n = 259$) | HbA _{1c} \downarrow 1.9% once weekly group vs 1.5% in BID group | 0.002 | 2 |
| Exenatide extended-release | RCT, exe 2 mg once weekly vs sita 100 mg QD vs pio 45 mg QD ($n = 491$) | HbA _{1c} \downarrow 1.5% exe group, 0.9% sita group, 1.2% pio group | <0.001 exe vs sita; 0.02 exe vs pio | 3 |
| Exenatide extended-release | RCT, exe 2 mg once weekly vs insulin glargine titrated to FBG 72–99 mg/dL ($n = 456$) | HbA _{1c} \downarrow 1.5% exe group vs 1.3% insulin glargine group | 0.01 | 4 |
| Exenatide extended-release | RCT, exe 2 mg once weekly vs met 2000 mg/d vs pio 45 mg/d vs sita 100 mg/d ($n = 820$) | HbA _{1c} \downarrow 1.53% exe group, 1.48% met group, 1.63% pio group, 1.15% sita group | 0.62 exe vs met; 0.34 exe vs pio; <0.001 exe vs sita | 5 |
| Exenatide extended-release | RCT, exe 2 mg once weekly vs exe 10 μg BID ($n = 252$) | HbA _{1c} \downarrow 1.6% once weekly group vs 1.0% in BID group; FBG \downarrow 35 mg/dL once weekly group vs 12 mg/dL BID group | <0.001 ; <0.001 | 6 |
| Dapagliflozin | RCT, dapa 2.5, 5, or 10 mg vs pcb ($n = 474$) | HbA _{1c} \downarrow 0.58%–0.89% (decreases up to 2.88% in those with very high HbA _{1c}) | 0.005 cana 5 mg vs pcb; <0.001 cana 10 mg vs pcb | 7 |
| Dapagliflozin | RCT, dapa or glip plus met ($n = 800$) | HbA _{1c} \downarrow 0.52% in both groups, weight \downarrow 3.22 kg in dapa; \uparrow 1.44 kg glip | <0.001 (weight change) | 8 |
| Dapagliflozin | RCT, dapa, or pcb plus met ($n = 534$) | HbA _{1c} \downarrow 0.3% pcb, HbA _{1c} \downarrow 0.67% dapa 2.5 mg, HbA _{1c} \downarrow 0.7% dapa 5 mg, HbA _{1c} \downarrow 0.84% dapa 10 mg | <0.001 , <0.001 , <0.001 | 9 |
| Dapagliflozin | RCT, dapa, or pcb plus glim ($n = 597$) | HbA _{1c} \downarrow 0.13% pcb, HbA _{1c} \downarrow 0.58% dapa 2.5 mg, HbA _{1c} \downarrow 0.63% dapa 5 mg, HbA _{1c} \downarrow 0.82% dapa 10 mg | <0.001 , <0.001 , <0.001 | 10 |
| Dapagliflozin | RCT, dapa, or pcb plus pio ($n = 360$) | HbA _{1c} \downarrow 0.42% pcb, HbA _{1c} \downarrow 0.82% dapa 5 mg, HbA _{1c} \downarrow 0.97% dapa 10 mg | <0.001 , <0.001 | 11 |
| Dapagliflozin | RCT, dapa plus insulin ($n = 808$) | HbA _{1c} \downarrow 0.39% pcb, HbA _{1c} \downarrow 0.79%–0.96% dapa | <0.001 | 12 |
| Canagliflozin | Cana (various doses) added to met ($n = 451$) | HbA _{1c} \downarrow 0.7%–0.95% with addition of cana | All doses <0.001 | 13 |

\downarrow = decreased; \uparrow = increased; cana = canagliflozin; dapa = dapagliflozin; exe = exenatide; FBG = fasting blood glucose; glim = glimepiride; glip = glipizide; HbA_{1c} = hemoglobin A_{1c}; met = metformin; pcb = placebo; pio = pioglitazone; RCT = randomized controlled trial; sita = sitagliptin.

ized lifestyle counseling at each visit using the LEARN manual. The baseline weight was 116 kg, and the mean BMI was 42 kg/m².³⁵ The primary outcome was percentage of weight loss at week 52; analysis was by ITT with LOCF. The percentage of weight loss with phen-top CR 15 mg/92 mg was 10.9% compared with 5.1% with phen-top CR 3.75 mg/23 mg and 1.6% for placebo ($P < 0.001$ for both doses compared with placebo). Absolute weight loss based on least squares mean was 12.6 kg for phen-top CR 15 mg/92 mg, 6 kg for phen-top CR 3.75 mg/23 mg, and 1.8 kg for placebo. Both doses of phen-top CR reduced specific secondary outcomes, although phen-top 15 mg/92 mg was more efficacious; the differences are of questionable clinical relevance.³⁵

The CONQUER study (Effects of Low-Dose, Controlled-Release, Phentermine Plus Topiramate Combination on Weight and Associated Comorbidities in Overweight and Obese Adults) included people with a BMI of 27 to 45 kg/m² or those with type 2 diabetes with any BMI. To be eligible, patients were required to have 2 of the following: elevated blood pressure or taking 2 antihypertensive agents, elevated triglyceride levels or use of 2 lipid drugs, impaired fasting glucose or diagnosis with type 2 diabetes treated with only lifestyle or metformin, or a waist circumference of >102 cm for men and >88 cm for women.³⁶

Participants were stratified based on sex and whether they had type 2 diabetes and were randomized to phen-top CR 7.5 mg/46 mg (n=498), phen-top CR 15 mg/92 mg (n=995), or placebo (n=994); phen-top CR doses were initiated at 3.75 mg/15 mg and titrated

at weekly intervals by 3.75 mg/15 mg to the target dose, which was continued for 52 weeks. All patients received standardized lifestyle and nutritional counseling at each study visit using the LEARN manual. At baseline the mean baseline weight was 101 kg, and the mean BMI 36 kg/m².³⁶

The coprimary outcome of the CONQUER study was mean percentage change in weight and percentage of patients achieving at least 5% weight loss; analysis was by ITT with LOCF. The percentage weight loss (calculated by least squares mean) was 7.8% (8.1 kg) with phen-top CR 7.5 mg/46 mg, 9.8% (10.2 kg) for phen-top CR 15 mg/92 mg, and 1.2% (1.8 kg) for placebo ($P < 0.001$ for both doses vs placebo). Approximately 21%, 62%, and 70% achieved at least 5% weight loss while receiving placebo, phen-top CR 7.5 mg/46 mg, and phen-top CR 15 mg/92 mg, respectively ($P < 0.001$ for both doses vs placebo). Treatment with phen-top CR improved blood pressure, HDL-C, triglyceride, HbA_{1c}, and fasting glucose compared with placebo ($P < 0.05$ for all comparisons), although the absolute differences were often of questionable clinical significance.³⁶

The SEQUEL study was a 1-year extension of the CONQUER trial; patients were only eligible if they completed the CONQUER study on treatment and complied with protocol requirements.³⁴ Baseline characteristics of SEQUEL were similar to those in CONQUER, the mean weight was 102 kg, and the mean BMI was 36 kg/m². Patients continued their randomized treatment from CONQUER for an additional 52 weeks; 227 received placebo, 153 received phen-top CR 7.5 mg/46 mg, and 295 received phen-top CR 15 mg/92

Table III. Dyslipidemia Clinical Trials Summary.

| Drug | Design and Intervention | Results | P | Reference |
|-----------------|---|--|--|-----------|
| Icosapent ethyl | RCT, 4 g/d vs placebo 2 g/d vs placebo (n = 153) | 33.1% reduction in triglycerides; 19.7% reduction in triglycerides | <0.001 icosapent ethyl 4 g/d vs placebo; 0.005 icosapent ethyl 2 g/d vs placebo | 16 |
| Icosapent ethyl | RCT, 4 g/d vs placebo; 2 g/d vs placebo (n = 702) | 21.5% decrease in triglycerides; 5.6% decrease in triglycerides | <0.001 icosapent ethyl 4 g/d vs placebo; <0.001 icosapent ethyl 2 g/d vs placebo | 17 |

RCT = randomized controlled trial.

mg. A second primary outcome, mean percentage change in weight and percentage of participants achieving at least 5% weight loss, was based on results at 104 weeks; analysis was conducted in the ITT population with the LOCF.³⁷

In the SEQUEL study, percentage weight loss (calculated by least squares mean) with placebo was 1.8% (2.1 kg) compared with 9.3% (9.6 kg) for phen-top CR 7.5 mg/15 mg and 10.5% (10.9 kg)

with phen-top CR 15 mg/92 mg ($P < 0.001$ for both doses vs placebo). Nearly 80% of participants receiving phen-top CR 15 mg/92 mg attained 5% weight loss compared to 75% receiving phen-top CR 7.5 mg/46 mg and 30% receiving placebo ($P < 0.001$ for both doses compared with placebo). Results of SEQUEL indicate that weight loss is maintained during a second year of treatment. Because only the patients completing CONQUER and complying with

Table IV. Obesity Clinical Trials Summary.

| Drug | Design and Intervention | Results | P | Reference |
|------------------------|---|---|---------------------------------------|-----------|
| Lorcaserin | R, DB, PC; lor 10 BID, lor 10 QD, or pcb for 52 weeks | At 52 weeks weight loss of >5% of baseline weight occurred in 47.2% of lor 10 BID, 40.2% of lor 10 QD, and in 25% of pcb patients | <0.001 for both doses vs pcb | 24 |
| Lorcaserin | R, DB, PC; lor 10 mg BID or pcb for 52 weeks; pcb continued for 52 weeks, lor randomized in 2:1 ratio to continue lor 10 mg BID or pcb for 52 weeks | At 52 weeks weight loss of >5% of baseline weight occurred in 47.5% of lor 10 BID and 20.3% of pcb patients | <0.001 | 25 |
| Lorcaserin | R, DB, PC; lor 10 BID, lor 10 QD, or pcb for 52 weeks | At 52 weeks weight loss of >5% of baseline weight occurred in 37.5% of lor 10 BID, 44.7% of lor 10 QD, and 16.1% of pcb patients | <0.001 for both doses vs pcb | 26 |
| Phentermine-topiramate | R, DB, PC; P/T 15/92, P/T 3.75/23, or pcb for 52 weeks | Percentage of baseline weight lost at 52 weeks was 10.9% for P/T 15 mg/92 mg, 5.1% for P/T 3.75 mg/23 mg, and 1.6% for pcb | <0.001 for both doses compared to pcb | 30 |
| Phentermine-topiramate | R, DB, PC; P/T 7.5 mg/46 mg, P/T 15 mg/92 mg, or pcb for 52 weeks | Percentage of baseline weight lost at 52 weeks was 9.8% for P/T 15 mg/92 mg, 7.8% for P/T 7.5 mg/46 mg, and 1.2% for pcb | <0.001 for both doses compared to pcb | 31 |
| Phentermine-topiramate | R, DB, PC extension of Gadde et al ³⁶ ; continued same treatment for 52 weeks | Percentage of baseline weight lost at 104 weeks was 10.5% for P/T 15 mg/92 mg, 9.3% for P/T 7.5 mg/46 mg, and 1.8% for pcb | <0.001 for both doses vs pcb | 32 |

BID = twice daily; DB = double blind; lor = lorcaserin; PC = placebo controlled; pcb = placebo; P/T = phentermine-topiramate controlled-release; QD = once daily; R = randomized.

protocol requirements were eligible for SEQUEL, the results could be biased because only the adherent patients and those likely to be satisfied with treatment potentially continued with the study.³⁷

On the basis of the results of these studies, phen-top CR is approved for the treatment of obesity in patients with a BMI >30 kg/m² or a BMI >27 kg/m² with at least one weight-related comorbidity, such as hypertension, type 2 diabetes mellitus, or dyslipidemia, in addition to a reduced calorie diet and increased physical activity.³⁵⁻³⁷ Phen-top CR therapy is started at 3.75 mg/23 mg, taken QD in the morning, and after 14 days it can be increased to 7.5 mg/46 mg. If after 12 weeks at least 3% weight loss has not been achieved, use of the drug can be discontinued or the dose can be increased to 11.25 mg/69 mg for 14 days followed by a final dose increase to 15 mg/92 mg. Weight loss should be evaluated after an additional 12 weeks, and if 5% weight loss is not achieved therapy should be discontinued. The most common adverse reactions include paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth.³¹ Phen-top CR is estimated to cost approximately \$6 per day.³³

Currently, it is unclear how these new agents fit into the treatment armamentarium of obesity. In patients with type 2 diabetes bariatric surgery has proven to be more beneficial compared with intensive medical therapy, although phentermine, topiramate, or lorcaserin were not used.³⁸ Therefore, it is unknown how these agents would compare with bariatric surgery. Because nearly all of the studies included mostly white females, further study in more diverse subgroups is warranted to ensure the tolerability and efficacy are maintained in a wide range of patient populations.

The biggest barrier to the widespread use of these agents will likely be their cost. At an estimated yearly cost of nearly \$1500 for lorcaserin and nearly \$2200 for phen-top CR, the cost for each kilogram lost is approximately \$265 and \$180 for lorcaserin and phen-top CR, respectively.³³ Given the substantial cost and the potential for adverse effects and drug interactions, it is unknown whether the risks and cost of therapy are outweighed by the long-term benefits of weight loss without prospective studies investigating CVD risk reduction. Long-term outcomes, such as CVD and mortality, should be evaluated to determine whether these agents produce any reductions in clinical outcomes to offset their substantial cost.

CONCLUSION

Diabetes, dyslipidemia, and obesity are some of the most challenging conditions to manage in the outpatient setting. New and future medications offer clinicians additional therapeutic options, although they

Table V. Comparative Medication Costs.

| Medication | WAC Cost, \$ (30-Day Supply) ^a |
|---|---|
| Diabetes | |
| Metformin 500 mg | 10.00 |
| Glyburide 10 mg | 15.00 |
| Glipizide XL 20 mg | 75.00 |
| Pioglitazone 45 mg | 209.27 |
| Exenatide ^b 10 µg | 315.25 |
| Liraglutide ^c 1.8 mg | 303.34 |
| Sitagliptin ^d 100 mg | 223.81 |
| Saxagliptin ^e 5 mg | 223.79 |
| Linagliptin ^f 5 mg | 223.81 |
| Exenatide (extended release) ^g 2 mg | 349.32 |
| Dyslipidemia | |
| Pravastatin 40 mg | 10.20 |
| Lovastatin 40 mg | 9.60 |
| Simvastatin 40 mg | 11.13 |
| Atorvastatin 40 mg | 18.30 |
| Rosuvastatin ^h 40 mg | 152.40 |
| Niacin 500 mg | 1.44 |
| Niaspan 1000 mg | 156.6 |
| Fenofibrate 145 mg | 135.00 |
| Omega-3-acid ethyl esters ⁱ 1 g | 184.10 |
| ω3-fish oils 2 g | 40.75 |
| Gemfibrozil 600 mg | 15.00 |
| Cholestyramine 4 g | 18.00 |
| Ezetimibe ^j 10 mg | 141.60 |
| Obesity | |
| Orlistat ^k (orlistat) 120 mg | 395.45 |
| Phentermine 37.5 mg | 18.60 |
| Diethylpropion IR 25 mg | 19.80 |
| Diethylpropion ER 75 mg | 25.20 |
| Phendimetrazine IR 35 mg | 11.703 |
| Phendimetrazine ER 105 mg | 22.20 |
| Phentermine and Topiramate extended-release ^l 15 mg/92 mg | 183.90 |

WAC = wholesale acquisition cost.

^aPricing obtained from www.rpriceverify.com on December 5, 2012.

^bByetta™ (Amylin Pharmaceuticals, Inc, San Diego, California).

^cVictoza™ (Novo Nordisk Inc., Princeton, New Jersey).

^dJanuvia™ (MERCK SHARP & DOHME LTD, Cramlington, Northumberland, United Kingdom).

^eOnglyza™ (Bristol-Myers Squibb Company, Princeton, New Jersey).

^fTradjenta™ (Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, Connecticut).

^gBydureon™ (Amylin Pharmaceuticals, Inc, San Diego, California).

^hCrestor™ (AstraZeneca Pharmaceuticals LP., Wilmington, Delaware).

ⁱLovaza™ (GlaxoSmithKline, Research Triangle Park, North Carolina).

^jZetia™ (Merck/Schering-Plough Pharmaceuticals North Wales, Pennsylvania).

^kXenical™ (Genentech Inc, South San Francisco, California).

^lQsymia™ (VIVUS Inc, Mountain View, California).

may or may not lead to improved control (Tables II, III, and IV). For type 2 diabetes, exenatide extended-release has fewer adverse effects and better efficacy than the daily exenatide. The new SGLT2 inhibitor class offers a unique mechanism of action, mean efficacy (HbA_{1c} reductions near 1%), and seemingly few adverse effects. The SGLT2 inhibitors appear to offer some benefits and will likely be used as one of several second-line options. Long-term tolerability and efficacy data are needed to more precisely define their role. With respect to dyslipidemia, icosapent ethyl effectively lowers triglyceride levels by ~20% to 45% (depending on baseline triglycerides), with little effect on LDL-C. Lorcaserin is a novel anorexic agent that results in an ~5.5-kg mean weight loss when used for 1 to 2 years. Phen-top reduces weight by a mean of 12.2 kg, which was maintained for 1 to 2 years of continued treatment. Both antiobesity agents are approved for patients with a BMI of >30 kg/m² or >27 kg/m² with at least one weight-related comorbidity. Although all these agents certainly add to our armamentarium, at this point it does not appear that any of them offer significant advantages over currently available options. They will likely also be rather expensive medications as well, likely preventing them from being used as first-line agents in most patients. Table V provides a summary of comparative costs for various medications for these disease states. Further studies will help to more clearly define their roles in therapy.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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