

AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 10: Obesity **Potential High Impact Interventions Report**

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHS29020100006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual Topic Profiles are developed for technologies and programs that appear to be closer to diffusion into practice in the United States. Drafts of those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify those interventions that experts deem, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually, and topics included may change depending on expert comments received on interventions issued for comment during the preceding six months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in the horizon scanning, assessing the leads for topics, or provide opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor target technologies and innovations in health care and to create an inventory of target technologies that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is the identification and monitoring of new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is the analysis of the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future utilization and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling a profile on topics and issuing topic profile drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COI).

Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the high impact potential designation. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the nine topics for which (1) preliminary phase III data on drug topics and phase II data on device or procedure topics were available; (2) information was compiled by November 2011 in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and November 1, 2011. (A total of 19 topics in this priority area were being tracked in the system as of November 2011.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present two summaries of five topics (indicated below by an asterisk) that emerged as potential high impact on the basis of experts’ comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 10: Obesity	
1.	*Controlled release phentermine/topiramate (Qnexa) for treatment of obesity
2.	*EndoBarrier Endoluminal Sleeve for treatment of obesity
3.	Full Sense Bariatric Device for treatment of morbid obesity
4.	*Liraglutide (Victoza) for treatment of obesity
5.	*Lorcaserin (Lorcass) for treatment of obesity
6.	Maestro vagus nerve block system for treatment of morbid obesity
7.	Methionine aminopeptidase 2 inhibitor (ZGN-433) for treatment of obesity
8.	*Naltrexone and bupropion HCL (Contrave) for treatment of obesity*
9.	Tesofensine for treatment of obesity

Discussion

According to the U.S. Centers for Disease Control and Prevention (CDC), the prevalence of overweight and obesity in the U.S. increased from 15% of adults in 1980 to approximately 34% of adults in 2006. By 2008, 68% of the population was deemed overweight, with half of that number being categorized as obese. Although this trend has stabilized in the past few years, CDC reports that

prevalence among children continues to increase, with approximately a third of all children 19 years of age and younger being considered overweight or obese. More than 15 million adults have a body mass index $>40 \text{ kg/m}^2$ or a BMI of 35 kg/m^2 and comorbidities. Obesity is a major contributor to many diseases including blood clots, coronary artery disease, dyslipidemia, hypertension, sleep apnea, strokes, and type 2 diabetes mellitus (T2DM). Obesity or excess fat also increases the risk of several types of cancers including colorectal, endometrial, esophageal, renal, and postmenopausal breast cancers. CDC also reported that U.S. medical expenditures attributed to obesity totaled about \$147 billion in 2008 dollars and stated that taxpayers, through Medicare and Medicaid programs, paid more than half of these costs. Based on current standards, individuals with BMI <30 but $>25 \text{ kg/m}^2$ are considered overweight. Individuals with a BMI $>30 \text{ kg/m}^2$ are considered obese. Individuals with BMI $>35 \text{ kg/m}^2$ or BMI $>40 \text{ kg/m}^2$ are considered severely obese and morbidly obese, respectively.

In addition, waist circumference, which measures abdominal fat, predicts obesity-related risk factors. Men with a waist of more than 40 inches and women with a waist measuring greater than 35 inches are at increased risk for obesity-related health consequences. Current data suggest that risk of overweight/obesity-related morbidity and mortality increases progressively with BMI $>25 \text{ kg/m}^2$. Research indicates that individuals can reduce their risk of obesity-related adverse health conditions by decreasing their total body weight by approximately 10%.

Only one surgical treatment has definitively demonstrated long-term efficacy for morbidly obese patients (gastric bypass surgery) and only one pharmacotherapy is currently available for long-term treatment of overweight and obesity. But the surgery has significant associated risks and mortality; and the drug therapy has undesired side effects and limited efficacy for sufficient weight loss. Additional treatment options are highly desired. Some new options are in development, but have had a long and sometimes circuitous path to marketing approval.

Antiobesity Drugs for Treatment of Obesity

- **Key Facts:** Three drugs are in phase III development for the treatment of obesity, each posing a different mechanism of action, but their approval was rejected by the U.S. Food and Drug Administration (FDA) and revised submissions are underway: phentermine/topiramate combination therapy (Qnexa®, Vivus, Inc., Mountain View, CA), lorcaserin (Lorcass®, Arena Pharmaceuticals, Inc., San Diego, CA), and naltrexone HCl/bupropion HCl combination therapy (Contrave®, Orexigen Therapeutics, Inc., La Jolla, CA in collaboration with Takeda Pharmaceutical Co., Ltd., Osaka, Japan). Concerns over lack of FDA-approved pharmacotherapies for the treatment of obesity were expressed in September 2011 by the U.S. Congressional Committee on Appropriations. The committee stated “the lack of obesity medications is a significant unmet medical need.” The direction by this committee to have FDA develop a pathway in support of development of antiobesity treatments by March 30, 2012, prompted the FDA to work closely with these manufacturers. In addition, liraglutide (Victoza®, Novo Nordisk AS, Bagsvaerd, Denmark), an FDA-approved drug for management of type 2 diabetes mellitus appears to be of interest for off-label use for treatment of obesity. Phentermine/topiramate is a controlled-release formulation of two separate FDA-approved drugs. This drug combination acts in the central nervous system as an appetite suppressant.

Lorcaserin is an investigational 5-hydroxytryptamine Type 2C (5-HT_{2C}) receptor agonist believed to selectively stimulate the 5-HT_{2C} serotonin receptors in the brain, which are involved in controlling appetite and metabolism. Naltrexone/bupropion combination drug is an oral, sustained-release drug intended to fight the body's tendency to regain weight after weight loss through the combined mechanism of bupropion, which activates

the pro-opiomelanocortin neurons in the brain to release a hormone called alpha-MSH, and naltrexone, which inhibits beta-endorphin, a natural opiate believed to increase food intake. Liraglutide is a synthetic analog of the peptide hormone glucagon-like peptide-1 (GLP-1), which has been shown to suppress appetite and energy intake as well as delay gastric emptying, which may induce a feeling of satiety

- **Key Expert Comments:** Experts generally expressed optimism about these interventions' ability to meet the need of obese patients for moderate weight loss, given the lack of effective interventions for the treatment of obesity and failure of dietary/lifestyle modifications among overweight individuals. Experts generally indicated that both patient and clinician acceptance would be high for these options, because the potential to eliminate long-term sequelae of obesity-related diseases is critically important. However, experts opined that invasiveness of treatments, such as liraglutide injection, and potential increase in per-patient costs of care might serve as barriers to acceptance for some patients because payers generally do not reimburse for antiobesity drugs.
- **Potential for High Impact:** High

EndoBarrier Endoluminal Sleeve for Excess Weight Loss and/or Treatment of Type 2 Diabetes

- **Key Facts:** Bariatric surgery is the only treatment that has been demonstrated to be effective for morbidly obese patients who do not respond to conservative treatments (e.g., diet, exercise). However, some super-morbidly obese patients are ineligible for surgery because of surgical risks and complications. The EndoBarrier® Endoluminal Sleeve (GI Dynamics, Inc., Lexington, MA) device might offer a potential alternative. It is a 60-cm impermeable sleeve that allows partially digested food leaving the stomach to move through the gastrointestinal tract without mixing with digestive enzymes or allowing nutrients to be absorbed through the intestinal walls. The device is deployed during a same-day procedure by means of a catheter routed through the esophagus into the stomach and small intestine. There, it is anchored with barbs that penetrate into the muscle wall. The device extends down through parts of the small intestine. The liner can be removed endoscopically using drawstrings that collapse the anchor stent barbs. The device has been on the market in Europe since 2009. Results of two European-based trials of the EndoBarrier device were recently published and new results from three studies were reported by the company in March 2011. The company intends to submit a premarket approval application to FDA, pending outcomes of ongoing trials. The device is commercially available in Australia. At least two large medical device companies have been reported to have invested in the ongoing development in the U.S.
- **Key Expert Comments:** Overall, experts believe that the EndoBarrier has significant potential to promote moderate, temporary weight loss, which might aid super-morbidly obese patients in achieving the required prebariatric surgery weight loss and improving diabetes-associated metabolic factors. However, experts were concerned about the treatment's side-effect profile and treatment-discontinuation rate, and they were generally skeptical of whether treatment might truly increase the percentage of patients who could go on to have successful bariatric surgery.
- **Potential for High Impact:** Lower range of high impact

Obesity Interventions

Intervention

Antiobesity drugs for treatment of obesity

The increasing prevalence of overweight and obese populations in the United States has generated a call for novel pharmacologic therapies aimed at weight reduction and maintenance when diet and exercise have failed. Expanded understanding of the human body's physiologic systems and pathways has increased interest in antiobesity drug development, with several innovative mechanisms of action under way that are intended to decrease food consumption, increase satiety, decrease fat absorption, increase metabolic activity, and increase energy expenditure. However, concerns over potential adverse events associated with antiobesity pharmacotherapies have significantly increased regulatory standards for approval, specifically regarding preapproval safety data and postmarket safety evaluation, set forth by the U.S. Food and Drug Administration (FDA).

Currently, orlistat, a pancreatic lipase inhibitor that blocks approximately one third of daily fat absorption, is the only FDA-approved antiobesity drug available for long-term use in the U.S. and for use in adolescents. Many patients discontinue treatment with orlistat because of its unpleasant side effects, namely oily spotting, flatulence, and fecal urgency. In May 2010, FDA approved a revised label for orlistat, relaying new safety information to health care professionals and patients about rare cases of severe liver injury associated with use of the drug.¹ In October 2010, Abbot Laboratories (Abbott Park, IL) voluntarily withdrew another antiobesity drug, sibutramine (Meridia®), upon FDA request after preliminary results of the therapy's SCOUT trial discovered risk of adverse cardiovascular events.²

Amid concerns over various adverse events, three drugs in late-phase development for the treatment of obesity, each posing a different mechanism of action, have been rejected by FDA since October 2010: phentermine/topiramate combination therapy (Qnexa®, Vivus, Inc., Mountain View, CA), lorcaserin (Arena Pharmaceuticals, Inc., San Diego, CA), and naltrexone /bupropion HCL combination therapy (Contrave®, Orexigen Therapeutics, Inc., La Jolla, CA, in collaboration with Takeda Pharmaceutical Co., Ltd., Osaka, Japan).³ Concerns over lack of FDA-approved pharmacotherapies for the treatment of obesity were expressed September 2011 by the U.S. Congressional Committee on Appropriations, stating "the lack of obesity medications is a significant unmet medical need."⁴ The direction by this committee to have the FDA develop a clearer pathway to market for antiobesity treatments by March 30, 2012, prompted FDA to reapproach these manufacturers to find a way forward. This summary examines these three drugs in addition to liraglutide (Victoza®, Novo Nordisk AS, Bagsvaerd, Denmark), an FDA-approved drug for management of type 2 diabetes mellitus (T2DM) that clinicians might consider for off-label use in the treatment of obesity.

Naltrexone/bupropion combination therapy

Naltrexone/bupropion combination drug is an oral, sustained-release formulation intended to counteract the tendency to regain weight after weight loss. The drug is thought to have a combined mechanism in which bupropion activates the pro-opiomelanocortin (POMC) neurons in the brain to release a hormone called alpha-MSH, and naltrexone inhibits beta-endorphin, a natural opiate believed to increase food intake.⁵ Bupropion is responsible for controlling hunger and burning more energy.⁵ By blocking beta-endorphin, naltrexone enhances POMC-stimulating effects of bupropion.⁵ Using a mouse model, investigators reported that bupropion and naltrexone together increase the firing frequency of POMC neurons in the brain and that this firing frequency increases when the drugs are

combined.⁵ Dosages of combined naltrexone 32 mg /bupropion 360 mg/day (NB32 or Contrave32) and naltrexone 16 mg/bupropion 360 mg/day (NB16 or Contrave16) have been evaluated in clinical trials.

In 2010, Greenway and colleagues announced results from a 56-week phase III trial (COR-I) evaluating NB32 and NB16 compared with placebo. Obese patients (n = 1,742) were randomly assigned to one of three groups in a 1:1:1 ratio. The authors concluded, "Treatment with Contrave resulted in significant improvements over placebo in waist circumference, insulin resistance, HDL cholesterol, triglycerides, and hsCRP, which are well-known and accepted measures of cardiometabolic risk."⁶ Results of NB32 administration showed "34% of patients completing the study lost at least 10% of their body weight as compared to 11% on placebo (p <0.0001); patients taking Contrave showed significant improvements in important secondary endpoints: waist circumference (-6.2 cm on Contrave32 vs. -2.5 cm on placebo), insulin resistance (-20.2% vs. -5.9%), HDL cholesterol (+8.0% vs. +0.8%), triglycerides (-12.7% vs. -3.1%) and hsCRP (-29.0% vs. -16.7%) compared to patients taking placebo on an ITT basis."⁶ The most common adverse events reported were nausea, headache, upper respiratory tract infection, and constipation.

On January 31, 2011, FDA issued a complete response letter to the Contrave new drug application (NDA). FDA expressed concerns about the long-term cardiovascular safety profile in the overweight and obese population. The letter stated that "before your application can be approved, you must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile."⁷ In June 2011, the manufacturer temporarily suspended production of naltrexone/bupropion due to the new requirements for the regulatory pathway for this drug. The manufacturer met with FDA's Office of New Drugs in September 2011, during which FDA clarified a pathway to marketing approval.⁸ The cardiovascular outcomes trial required by FDA is not scheduled to begin until the first half of 2012; the manufacturer anticipates submitting results and having the drug become eligible for approval sometime in 2014.⁹

Lorcaserin

Lorcaserin (Arena Pharmaceuticals, Inc., San Diego, CA) is under study as a 5-HT_{2C} agonist for weight loss. It is believed to selectively stimulate the 5-HT_{2C} serotonin receptors in the brain, which are involved in controlling appetite and metabolism.¹⁰ The key mechanism of action for lorcaserin is its high selectivity for 5-HT_{2C} receptor and its inability to activate the 5-HT_{2B} receptor. However, the 5-HT_{2B} receptor has been associated with cardiac valvular disease in other nonselective serotonergic weight-loss drugs.¹¹ Investigators reported results from phase III trials that patients treated with twice daily lorcaserin (10 mg) had greater weight loss than patients receiving placebo. They reported improvements in fasting insulin and glucose levels and blood pressure for lorcaserin patients compared to placebo overall.¹² Lorcaserin is a self-administered oral tablet.

In May 2011, Arena presented meta-analyses of the BLOOM, BLOSSOM, and BLOOM-DM phase III trials (double-blind, randomized, placebo-controlled) evaluating efficacy and safety of lorcaserin compared with placebo. The investigators reported that, "At one year, using Modified Intent-to-Treat with Last Observation Carried Forward analysis (MITT-LOCF) of the integrated results, 46.3% of lorcaserin 10 mg twice daily (BID) patients and 40.6% of lorcaserin 10 mg once daily (QD) patients achieved at least 5% weight loss, compared to 22.1% of patients on placebo, and 22.0% of lorcaserin 10 mg BID patients and 17.3% of lorcaserin 10 mg QD patients achieved at least 10% weight loss, compared to 8.3% of patients on placebo. Of the patients completing year one of the trials, 62.3% of lorcaserin 10 mg BID patients and 52.8% of lorcaserin 10 mg QD patients achieved at least 5% weight loss, compared to 32.0% of patients on placebo; and 33.5% of lorcaserin 10 mg BID

patients and 25.5% of lorcaserin 10 mg QD patients achieved at least 10% weight loss, compared to 13.8% of patients on placebo.”¹³

In October 2010, FDA recommended that the final data from the BLOOM-DM study be reported and indicated that further studies might be needed. FDA also asked for an independent pathology report to show that the drug's increased risk of astrocytoma in rats does not translate into risk for humans. In December 2010, Arena Pharmaceuticals announced a plan to resubmit the lorcaserin NDA by the end of 2011.¹⁴ As of November, 2011, the manufacturer had not yet resubmitted the NDA.

Phentermine/Topiramate

Phentermine/topiramate (Qnexa®, Vivus, Inc., Mountain View, CA) is a controlled-release formulation of two separate FDA-approved drugs. This drug combination acts on the central nervous system as an appetite suppressant.¹⁵ Phentermine is a central norepinephrine-releasing drug that was approved by FDA in 1959 as an appetite suppressant for short-term (3 months or less) treatment of obesity at a dose of 37.5 mg/day.^{16,17} Topiramate is a gamma aminobutyric acid agonist that was approved by FDA in 1996 for the treatment of epilepsy at a dose of approximately 400 mg/day and has been known to have weight loss as a side effect.^{16,17} Topiramate was studied as a monotherapy for treatment of obesity; however, dose-dependent neuropsychiatric adverse events precluded further study.¹⁶ By combining the effects of a low dose of each medication in a single treatment, Phentermine/topiramate might promote weight loss while avoiding side effects potentially caused by high doses of either drug. The phentermine plus topiramate combination is administered daily as an oral medication.¹⁵ In late-stage clinical trials, phentermine plus topiramate was administered at three different dose levels: a low dose of phentermine 3.75 mg plus topiramate 23 mg; a middle dose of phentermine 7.5 mg plus topiramate 46 mg; and a high dose of phentermine 15 mg plus topiramate 92 mg.¹⁶

In 2011, Allison and colleagues announced results from a 56-week clinical trial (EQUIP) evaluating the safety and efficacy of phentermine/topiramate in 1,267 morbidly obese patients. The authors reported, “Least-squares (LS) mean weight loss for phentermine/topiramate patients who completed the EQUIP study was 14.4% and 6.7% with top-dose phentermine/topiramate and low-dose phentermine/topiramate, respectively, compared to 2.1% in the placebo group ($p < 0.0001$); in the ITT-LOCF analysis, LS mean percent weight loss at week 56 was 10.0% and 5.1% for the top and low dose, respectively, as compared to 1.6% for the placebo group ($p < 0.00010$).”¹⁸ The authors also reported that among patients who completed top-dose treatment of phentermine/topiramate, “83.5% lost $\geq 5\%$; 67.7% lost $\geq 10\%$; and 48.1% lost $\geq 15\%$ of their baseline weight.”¹⁸ Common adverse events reported in this study were paresthesia (tingling), dysgeusia (taste alteration), and xerostomia (dry mouth).

In October 2011, the manufacturer announced the resubmission of its NDA to FDA after a September 2011 meeting with FDA about next steps.¹⁹ The resubmission presents a new contraindication for “women of childbearing potential.” In November 2011, FDA accepted the revised NDA with a decision date set for April 17, 2012.²⁰

Liraglutide

Liraglutide (Victoza®, Novo Nordisk AS, Bagsvaerd, Denmark) is a synthetic analog of the peptide hormone glucagon-like peptide-1 (GLP-1), which has been shown to suppress appetite and energy intake as well as delay gastric emptying, which may induce a feeling of satiety.²¹ Endogenous human GLP-1 has a short half-life (1 to 2 minutes); however, liraglutide has been modified to allow binding to serum albumin, which increases its half-life to approximately 13 hours.²¹ Liraglutide is an approved treatment for management of blood glucose levels in patients in whom T2DM has been

diagnosed.²² The drug is known to aid blood glucose control by stimulating the release of insulin and lowering glucagon secretion in response to high glucose levels.²² Additionally, during studies in patients with T2DM, liraglutide was reported to lead to a dose-dependent weight loss.²¹ Liraglutide is administered once daily via subcutaneous injection using an automatic injection pen.²¹ In clinical trials, liraglutide was self-administered in daily doses of 1.2 to 3.0 mg.²¹

Astrup and colleagues (2009) presented data from a study evaluating once daily liraglutide injection when compared to thrice daily orlistat or placebo in 564 patients diagnosed as obese with a BMI between 30 and 40 kg/m². The investigators concluded,

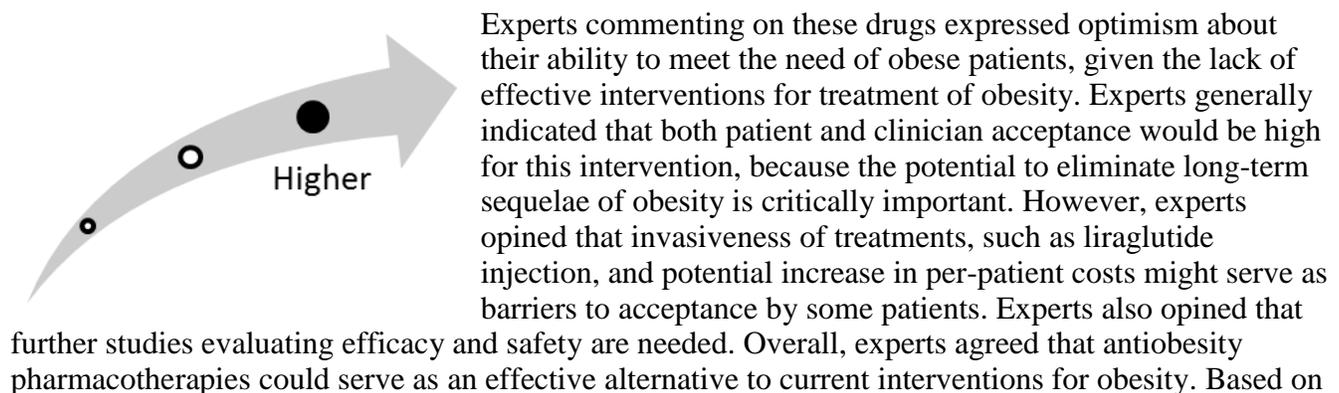
“Participants on liraglutide lost significantly more weight than did those on placebo (p = 0.003 for liraglutide 1.2 mg and p <0.0001 for liraglutide 1.8 to 3.0 mg) and orlistat (p = 0.003 for liraglutide 2.4 mg and p <0.0001 for liraglutide 3.0 mg). Mean weight loss with liraglutide 1.2 to 3.0 mg was 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg compared with 2.8 kg with placebo and 4.1 kg with orlistat, and was 2.1 kg (95% CI 0.6 to 3.6) to 4.4 kg (95% CI 2.9 to 6.0) greater than that with placebo. More individuals (76%, n = 70) lost more than 5% weight with liraglutide 3.0 mg than with placebo (30%, n = 29) or orlistat (44%, n = 42).”²¹

Since February 2010, Novo Nordisk has marketed the drug for treatment of T2DM to aid blood glucose control in combination with diet and exercise.²² Thus, liraglutide is not currently marketed as an obesity treatment, but could potentially be used off-label for weight management. A survey published in January 2011 suggests wide off-label use for treatment of obesity.²³ That survey of primary care physicians suggested that use of both liraglutide and a second GLP-1 analog, exenatide (Byetta®; Amylin Pharmaceuticals, Inc., San Diego, CA, and Eli Lilly and Co., Indianapolis, IN) is already well established. Approximately one third of the surveyed primary care physicians listed one of the GLP-1 analogs as the obesity drug they perceive as being most efficacious.²³

Clinical Pathway at Point of This Intervention

Patients are usually evaluated for obesity in a primary care setting. Height and weight are measured and used to calculate body mass index (BMI). Individuals with a BMI ≥ 30 kg/m² are classified obese.²⁴ Obese individuals are screened for other comorbid conditions, such as diabetes and hypothyroidism, that may influence treatment decisions and outcomes.²⁴ Medication use must also be assessed because some drugs, such as oral contraceptives, certain antipsychotics, and antidiabetes medicines may interfere with weight loss or contribute to excessive weight gain.^{1,25} Patients with a BMI ≥ 30 kg/m² or more or a BMI ≥ 30 kg/m² with comorbid obesity-related risk factors or diseases (such as hypertension, dyslipidemia, coronary heart disease, type 2 diabetes and sleep apnea) may be candidates for drug therapy.^{1,25} Drug therapy is typically offered in conjunction with a program of physical activity, nutrition counseling, and behavior management.²⁵

Figure 1. Overall High Impact Potential: Antiobesity drugs for treatment of obesity



this input, our overall assessment is that these interventions are in the higher end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on phentermine/topiramate.²⁶⁻³² Perspectives on three additional anti-obesity therapies (lorcaserin, naltrexone/bupropion, liraglutide) were received from a total of 20 experts—seven for lorcaserin, six for naltrexone/bupropion, seven for liraglutide.³³⁻⁵² Given the phase of the regulatory process for phentermine/topiramate, expert comments are more narrowly focused on this intervention. Expert opinions on the other pharmacotherapies included herein are added where comments apply.

All experts generally indicated that these antiobesity therapies have high potential to meet a significant unmet need in obesity treatment. One clinical expert commenting on phentermine/topiramate explained the importance of incorporating novel pharmacotherapies, stating, “Current treatments such as lifestyle changes are not effective since most people are unable and unwilling to sustain them; most physicians are not well versed in nutrition/physical activity interventions and are often reluctant to promote them to their patients because their time is not reimbursed.”³⁰

Experts were mixed regarding the potential for these interventions to significantly improve patient health outcomes. While several experts agreed the different underlying mechanisms of action for these antiobesity agents are sound, other experts expressed concern about limited available safety and efficacy data and adverse events profiles for several of these agents. For example, one clinical expert opined that the weight loss percentage of 8.0% to 8.9% reported in a study for naltrexone/bupropion at 56 weeks was marginal for obese and morbidly obese patients, leaving this expert skeptical of this intervention’s ability to improve patient outcomes. One research expert questioned whether weight loss seen in patients using lorcaserin was permanent or even long-term, citing the need for further studies. Another expert with a research perspective expressed concern about adverse gastrointestinal events reported with use of liraglutide, citing that more serious adverse events might occur with an increase in liraglutide dosage. An expert with a research perspective opined that patients might be noncompliant with use of phentermine/topiramate if adverse events (i.e., tingling, dry mouth, constipation) prove to interfere with patient quality of life, thus impacting patient health outcomes.

While most experts agreed these interventions have the potential to significantly impact health disparities, opinions were mixed as to whether health disparities would be reduced or increased. Experts believe that if these antiobesity pharmacotherapies are proven to be safe and effective, this could significantly reduce disparities among the African-American and Hispanic populations that are most adversely impacted by obesity. Referring to phentermine/topiramate, one research expert commented, “It appears that morbid obesity is closely aligned with socio-economic status, so this pharmacotherapy could be a big player in diminishing health disparities in this group.”²⁷ However, several experts insisted that costs associated with antiobesity pharmacotherapies and potential third party payers’ unwillingness to cover these therapies might significantly increase health disparities.

A majority of experts agreed the potential for these interventions would not significantly disrupt the current health care delivery infrastructure. One clinical expert evaluating liraglutide’s potential impact on current delivery infrastructure stated, “Evaluation and prescribing of the medication in an outpatient setting would have little or no [disruption] to the current health care delivery infrastructure.”⁴⁹ However, the same expert suggested that a potential shift in infrastructure could occur if weight loss prevents long-term complications associated with obesity in this patient population. Three experts believe that antiobesity pharmacotherapies might reduce the need for

bariatric surgery in some patients, thus disrupting the current health care model for this patient population.

Experts generally agreed that the potential for clinician and patient acceptance of these interventions is high. One clinical expert stated, “Clinicians are frustrated by the difficulty in treating obesity effectively with the currently used modalities. They also are reluctant to spend time teaching patients about lifestyle changes since this intervention is often times not reimbursed.”⁴⁹ However, pertaining to liraglutide injections, two research experts indicated patients might be unwilling to self-administer injections of this therapy. Several experts mentioned the uncertainty of long-term adverse events as a potential barrier to patient acceptance of antiobesity pharmacotherapies.

Several experts highlighted the fact that antiobesity pharmacotherapies are typically not covered by third-party payers, and expected patients to have to bear the costs out of pocket. However, a majority of experts thought that reducing or eliminating long-term complications from obesity might ultimately reduce per-patient costs over time. Several experts even indicated that initial costs of using these pharmacotherapies might be less costly than undergoing bariatric surgery or other antiobesity surgical interventions.

Intervention

EndoBarrier endoluminal sleeve for excess weight loss and treatment of type 2 diabetes

Bariatric surgery is the only treatment that has been demonstrated to be effective for morbidly obese patients who do not respond to conservative treatments (e.g., diet, exercise). However, some super-morbidly obese patients who might otherwise benefit from bariatric surgery are ineligible because of surgical risks and limitations posed by the patients' large size, weight, and thickness of adipose tissue. In addition, preoperative weight loss is widely recognized as correlating with improved outcomes and reduction of diabetes-related risks in all bariatric surgery patients. Therefore, a need exists for minimally invasive treatments that could allow these super-obese patients to lose 5% to 10% of their excess body weight.

EndoBarrier Luminal Sleeve (GI Dynamics, Inc., Lexington, MA) is intended to address this need. The device is a 60-cm impermeable sleeve that allows chyme (partially digested food leaving the stomach) to move through the gastrointestinal (GI) tract without mixing with digestive enzymes or allowing nutrients to be absorbed through the intestinal walls.⁵³ It is inserted under general anesthesia using dynamic fluoroscopic imaging; however, it may be possible to implant the device with the patient under conscious sedation in the future.⁵³ When implanted, the EndoBarrier is anchored within the duodenal bulb (small area of the small intestine just outside of the stomach) by a 5.5-cm nitinol (alloy of nickel and titanium), self-expanding stent with barbs that penetrate into the muscular wall of the intestine.⁵³ The sleeve extends down through parts of the small intestine (duodenum and proximal jejunum) and is purported to mimic the effects of GI bypass surgery.⁵³ The device is intended to remain in place for 12 to 24 weeks, during which time the patient is on a liquid diet supplemented with multivitamins and proton pump inhibitors to control acid reflux.⁵³⁻⁵⁵ When weight loss is achieved, the device is removed endoscopically by collapsing the nitinol stent and withdrawing the device from the stomach up through the esophagus.⁵³ The EndoBarrier was cleared in 2009 for use in Europe. Results of two European-based trials of the EndoBarrier device were recently published,^{53,56} and new results from three studies were reported by the company in March 2011.⁵⁷ As of July 25, 2011, the system had been approved by the Australian Therapeutic Goods Administration for inclusion in its therapeutic goods registry for treatment of T2DM and obesity for up to 12 months.⁵⁸ The company has not yet submitted a premarket approval application in the U.S., pending outcomes of ongoing trials. At least two large device companies have been reported to have invested in its development in the U.S.

In one European-based trial, 30 patients with a mean body mass index (BMI) of 48.9 kg/m² underwent EndoBarrier implantation in conjunction with dietary restriction and were compared with 11 patients in a control group with a mean BMI of 47.4 kg/m² who underwent dietary restriction alone.⁵³ Researchers reported that implantation was successful in 26 of 30 patients; however, the device was removed after 12 weeks in four patients because of device migration, dislocation of the device anchor, sleeve obstruction, or continuous epigastric pain.⁵³ Researchers reported that for patients completing the 12-week study, mean excess weight loss was 19.0% in the EndoBarrier-treated group versus 6.9% in the control group ($p < 0.002$).⁵³ Adverse events were reported in 100% of patients in this study. The majority of these events were reported as abdominal pain and nausea during week 1 postimplant; however, 23% of patients were reported to have vomiting during week 1 after implantation, 50% of patients were reported to have pseudopolyp formation postexplantation, and 38.5% of patients were reported to have implant-site inflammation postexplantation.⁵³

In the second European trial, EndoBarrier implantation was attempted on 27 patients whose outcomes were compared with 29 patients who underwent a sham implantation.⁵⁶ Researchers reported

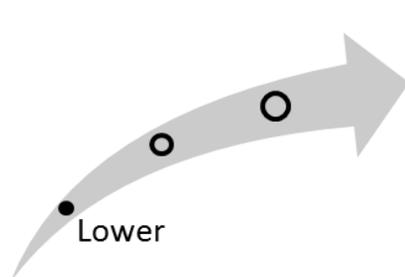
that of 21 patients in whom EndoBarrier was successfully implanted, eight terminated treatment before the full 12-week treatment because of GI bleeding (n = 3), abdominal pain (n = 2), nausea and vomiting (n = 2), or an illness unrelated to treatment (n = 1).⁵⁶ Thirteen EndoBarrier implanted patients and 24 sham patients completed the 12-week study with reported excess weight losses of 11.9% and 2.7% for the EndoBarrier and sham arms, respectively.⁵⁶

Results were presented on EndoBarrier's effects on two GI hormones (gut peptides glucagon-like peptide-1 [GLP-1] and peptide YY [PYY]) and other diabetes measures at the Second World Congress on Interventional Therapies for Type 2 Diabetes in March 2011. Jan Willem Greve, M.D., Ph.D., of the Gastrointestinal and Bariatric Surgery, Atrium Medical Center, Parkstad Heerlen, The Netherlands, reported that "EndoBarrier treatment offered rapid and long-lasting improvement in diabetes, and for the first time, demonstrated beneficial hormonal effects similar to surgical interventions such as Roux-en-Y gastric bypass." The study reported results on 17 obese patients with T2DM who received EndoBarrier for 24 weeks. Glycated hemoglobin A_{1c} (HbA_{1c}), glucose, insulin, GLP-1, and PYY were assessed. Patients were reported to have had a rapid increase and sustained insulin sensitivity; increased levels of both PYY and GLP-1 after 1-week implantation; a mean excess weight loss of 29.8%, reduction of HbA_{1c} from 8.4% at baseline to 7.0% after 6 months, and reduced intake of antidiabetic medications in 16 of 17 patients.⁵⁷ Data from two clinical trials⁵⁷ reported at the meeting were cited as evidence by the manufacturer that the EndoBarrier may be a candidate for the primary therapy of T2DM and obesity. E.G. Moura, M.D., Ph.D., director of endoscopy, Hospital das Clinicas, University of São Paulo, Brazil, evaluated the EndoBarrier in 22 patients with T2DM for 1 year. Patients' HbA_{1c} declined from 8.9% at baseline to 6.6% (p <0.0001); absolute weight loss was 20.2 kg (44 lb; p <0.0001), or 39% excess weight loss (p <0.0001). Also, metabolic functions including levels of insulin, cholesterol, low-density lipoprotein, and triglycerides levels normalized at 1 year. Alex Escalona, M.D., Department of Digestive Surgery, Pontificia Universidad Católica de Chile, Santiago, Chile, reported on weight loss and cardiometabolic factors in 46 obese patients 1 year after implantation. Patients achieved 20.0% total body weight loss (22.8 kg/50 lb) or 46.4% excess weight loss (p <0.0001), and total cholesterol and diastolic blood pressure declined significantly. A subset of six patients in the trial with T2DM achieved a mean HbA_{1c} reduction of 1.4% (p = 0.05; 7.9% at baseline to 6.5%).

Clinical Pathway at Point of This Intervention

The U.S. National Institutes of Health's Panel on Weight Loss recommended that all morbidly obese patients lose 10% of their excess body weight before bariatric surgery to help reduce surgical risks and postoperative complications.⁵⁹ However, currently available preoperative weight loss methods have demonstrated suboptimal success in morbidly obese patients. Losing weight through diet and exercise alone has often not been successful for this patient population.⁵⁹ Therefore, physicians may also recommend weight-loss medication, although that option is limited to only one approved drug.⁵⁹ Patients and clinicians would welcome the availability of other options for promoting preoperative weight loss in patients who have failed to lose weight using conservative treatment options.

Figure 2. Overall High Impact Potential: EndoBarrier endoluminal sleeve for excess weight loss



Overall, experts commenting on this intervention thought that while EndoBarrier appears to have potential to promote moderate, temporary weight loss, which could aid super-morbidly obese patients in achieving the required weight to undergo bariatric surgery and could also aid in improving diabetes-associated

metabolic factors. The potential was tempered by experts' significant concerns about adverse events reported thus far. They were also generally skeptical about whether treatment would truly increase the percentage of patients who would become eligible to undergo successful bariatric surgery. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this topic.⁶⁰⁻⁶⁵ Experts agreed that a significant unmet need exists for treatments that could aid morbidly obese patients in losing weight to become eligible for bariatric surgery or reducing the risks associated with diabetes, citing the increasing prevalence of obesity in the U.S. and the current lack of effective noninvasive weight-loss treatments for this population. In addition, experts agreed that the idea of inhibiting absorption in the intestine using an explantable impermeable barrier seems logical and noted that preliminary data on weight loss seems promising. However, multiple experts also noted the significant side effects and adverse events reported and the discontinuation rate, which they believe to be significant adverse factors. Additionally, several of these experts raised the concern that for a temporary treatment such as EndoBarrier to ultimately be effective, patients would need to transition to successful definitive bariatric surgery and that data on this outcome have not been reported. Lastly, one expert with a health systems background suggested that patients who would need to resort to EndoBarrier treatment to achieve prebariatric surgery weight loss might not be fully committed to the lifestyle changes required for successful subsequent bariatric surgery outcomes.

Regardless of the potential treatment efficacy, the EndoBarrier appears to have significant potential to increase scientific understanding of the GI system and the mechanism of action of bariatric surgeries, one clinical and one research expert commented; however, these observations may be more applicable to the potential of the device to control T2DM.

Most of the experts providing comments did not see potential for a shift in care setting, but one clinical expert and one researcher observed that bariatric procedures are generally surgical procedures whereas the EndoBarrier would likely be implanted in an endoscopy suite, which could involve capital equipment purchases for facilities that do not currently employ endoscopy in their bariatric practices. Experts also suggested that this could shift the type of specialist providing bariatric services from surgeons to GI physicians accustomed to doing endoscopy. If bariatric surgeons decide to perform the endoscopic procedure, experts opined, they would likely need training.

The expert opinions regarding treatment costs and reimbursement of EndoBarrier were highly variable. Several experts suggested that a temporary procedure such as the EndoBarrier would be unlikely to be reimbursed by third-party payers unless long-term outcomes on metabolic outcomes and transition to bypass surgery were reported. From a broader perspective, multiple experts noted that if EndoBarrier leads to patients undergoing successful bariatric surgery, the treatment could be cost effective because of a reduction in the costs associated with treating the effects of morbid obesity and diabetes.

As for whether patients were likely to opt for the EndoBarrier system, one clinical expert suggested that patients would be more likely to seek less invasive and cheaper alternatives for preoperative weight loss. Conversely, multiple experts noted that patients who would opt for EndoBarrier treatment would likely have exhausted conservative options. While multiple experts suggested that the potential for adverse side effects could deter patients from opting for EndoBarrier treatment, others noted that the target patient population would already be intending to undergo bariatric surgery, which carries significant risks, and such patients can have a high tolerance for risk.

Experts did not envision many barriers to physician adoption of EndoBarrier treatment, provided it is shown to be sufficiently safe and effective. Several experts noted some training would be involved in learning the implantation procedure, but did not think it would be a significant barrier.

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