AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 10: Obesity

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U.S. Department of Health and Human Services
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www.ahrq.gov

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Prepared by:
ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

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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. HHSA290201000006C). 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 close to diffusion into practice in the United States. 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 interventions that experts deemed, 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 6 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 horizon scanning, assessing the leads for topics, or providing 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 emerging technologies and innovations in health care and to create an inventory of interventions 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 identifying and monitoring 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 analyzing 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 use 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 email to: effectivehealthcare@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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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 identifying 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, review of more than 15,000 leads about potential topics has resulted in identification and tracking of about 1,600 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 950 topics are currently being actively tracked in the system.

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 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) 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 information on topics and issuing topic 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

(COIs). 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 designation of potentially high impact. 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 having potentially 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 four topics for which (1) preliminary phase III data for drugs, phase II or III data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled by September 21, 2012, in this priority area; *and* (3) we received six to nine sets of comments from experts between July 2011 and October 26, 2012. (Sixteen topics in this priority area were being tracked in the system as of October 26, 2012.) We present two summaries of two topics (indicated below by an asterisk) that emerged as having potential for high impact on the basis of experts' comments. 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

Topic	High-Impact Potential
1. * Controlled release phentermine-topiramate (Qsymia) for treatment of obesity	High
2. * EndoBarrier Endoluminal Sleeve for treatment of obesity and/or type 2 diabetes	Lower end of the potential high-impact range
3. Liraglutide (Victoza) for treatment of obesity	No high-impact potential at this time
4. Lorcaserin (Belviq) for treatment of obesity	No high-impact potential at this time

Discussion

Based on current definitions, individuals with body mass index (BMI) between 25 and 30 kg/m2 are considered overweight. Individuals with a BMI >30 kg/m2 are considered obese. Individuals with BMI >35 or >40 kg/m2 are considered severely obese and morbidly obese, respectively. According to the U.S. Centers for Disease Control and Prevention (CDC), the prevalence of obesity in the United States increased from 15% of adults in 1980 to about 34% of adults in 2006. By 2008, 68% of the population was deemed overweight, with half of that number being categorized as obese. More than 15 million adults have a body mass index >40 kg/m2 or a BMI of 35 kg/m2 and comorbidities. CDC reports that obesity prevalence among children continues to climb, with about one-third of all children 19 years of age and younger categorized as overweight or obese.

Obesity is a major contributor to many diseases, including type 2 diabetes mellitus (T2DM), cardiovascular disease, hypertension, and sleep apnea. Obesity also increases the risk of several types of cancer including colorectal, endometrial, esophageal, renal, and postmenopausal breast cancers.

Waist circumference, which measures abdominal fat, predicts obesity-related risk factors for disease. Men with a waist larger than 40 inches and women with a waist measuring more than 35 inches are at increased risk of developing obesity-related health consequences. Current data suggest that risk of overweight- and obesity-related morbidity and mortality increases as BMI increases past 25 kg/m^2. Research indicates that individuals can reduce their risk of obesity-related adverse health conditions by decreasing their total body weight by about 10%.

CDC also reported that researchers calculated 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.

Only one surgical treatment (gastric bypass surgery) has definitively demonstrated long-term efficacy for patients who are morbidly obese, and until recently, orlistat was the only U.S. Food and Drug Administration (FDA)-approved antiobesity pharmacotherapy available for long-term use in the United States. The surgery carries significant risks of morbidity and mortality, and the drug therapy has undesired side effects and limited efficacy in achieving 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.

Concerns over the dearth of pharmacotherapies approved by FDA for treating 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." This committee directed FDA to develop a pathway by March 30, 2012, to support development of antiobesity treatments. This prompted FDA to work more closely with manufacturers, eventually leading to the summer 2012 approvals of the two following antiobesity drugs:

- Combination phentermine-topiramate (Qsymia®, Vivus, Inc., Mountain View, CA)
- Lorcaserin (Belviq®, Arena Pharmaceuticals, Inc., San Diego, CA)

Additionally, liraglutide (Victoza®, Novo Nordisk a/s, Bagsvaerd, Denmark), an FDA-approved drug for management of T2DM, appears to be of interest for off-label use in treating obesity.

Two of these drugs considered for this iteration of the High Impact Report but not deemed high impact at this time by experts pose different mechanisms of action. They are lorcaserin and liraglutide.

Lorcaserin is a 5-hydroxytryptamine type 2C (5-HT2C) receptor agonist that selectively stimulates the 5-HT2C serotonin receptors in the brain, which are involved in controlling appetite and metabolism. FDA approved the drug on June 27, 2012, on the basis of three completed phase III trials. The approved indication is "as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial [BMI] of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)." The drug is classified by the U.S. Drug Enforcement Administration (DEA) as a Schedule IV drug, which means DEA will review FDA's recommendation and determine the final scheduling designation, a process that was estimated to take 4–6 months. Scheduling and product launch were expected by early 2013. No Risk Evaluation and Mitigation Strategy was required.

Liraglutide is a synthetic analog of the peptide hormone glucagon-like peptide-1, which has been shown to suppress appetite and energy intake as well as delay gastric emptying, which may induce a feeling of satiety. According to the company's drug pipeline, liraglutide 3 mg (NN8022) is

in phase III trials for treating obesity; a new drug application for this indication had not been submitted as of this writing.

Controlled-Release Phentermine-Topiramate (Qsymia) for Treatment of Obesity

- **Key Facts**: Before the summer of 2012, orlistat was the only FDA-approved antiobesity drug available for long-term use in the United States; it is still the only approved antiobesity drug for adolescent use. Many patients discontinue treatment with orlistat because of its unpleasant side effects. New drug treatment options are needed for obese patients seeking medical therapy for weight loss. Phentermine-topiramate is a controlled-release formulation of two separate FDA-approved drugs. This drug combination acts on the central nervous system as an appetite suppressant. 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. Topiramate is a gamma aminobutyric acid agonist that FDA approved in 1996 for treating epilepsy at a dose of approximately 400 mg/day, and it has been known to have weight loss as a side effect. Phentermine-topiramate in combination might promote weight loss while avoiding side effects potentially caused by high doses of either drug. FDA approved the drug on July 17, 2012, on the basis of two completed, phase III trials. Out-of-pocket expenses for phentermine-topiramate are between about $120 and $185 per month.
- **Key Expert Comments**: Experts generally expressed optimism about this intervention's ability to meet the need of patients who are obese for a medical solution for moderate weight loss, given the lack of pharmacotherapy interventions and failure of dietary and lifestyle modifications to achieve the needed weight loss among overweight individuals. Experts generally indicated that both patient and clinician acceptance would be high for this drug because the potential to eliminate long-term sequelae of obesity-related diseases is critically important. However, experts opined that the increase in per-patient costs of care might serve as a barrier to acceptance for some patients because payers generally do not reimburse for antiobesity drugs.
- **Potential for High Impact**: High

EndoBarrier Endoluminal Sleeve for Treatment of Obesity and/or Type 2 Diabetes

- **Key Facts**: Bariatric surgery is the only treatment that has been demonstrated to be effective for patients who are morbidly obese and whose condition does not respond to conservative treatments (e.g., diet, exercise). However, some patients who are super-morbidly obese are ineligible for surgery because of surgical risks and complications related to their weight. The EndoBarrier® Endoluminal Sleeve device (GI Dynamics, Inc., Lexington, MA) might offer an alternative to such patients. 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 and is commercially available in Australia. Results of two European-based trials of the EndoBarrier device were recently published and new results from three studies were reported by the manufacturer in March 2011. In October 2012, FDA approved the company's request to begin a 25-site pivotal trial for this device in treating obesity and T2DM. The company will consider submitting a premarket approval application following this trial's results. At least two large medical device companies have been reported to have invested in the ongoing development in the United Sates. No device or procedure cost information is available at this time.

- **Key Expert Comments**: Overall, experts thought that the EndoBarrier has significant potential to promote moderate, temporary weight loss, which might help patients who are super-morbidly obese to achieve the required prebariatric-surgery weight loss and improve 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 end of the high-potential-impact range

Obesity Interventions

Phentermine-Topiramate (Qsymia) 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. However, concerns over potential adverse events associated with antiobesity pharmacotherapies significantly increased the regulatory bar for gaining approval—specifically regarding preapproval safety data and postmarket safety evaluation—set forth by the U.S. Food and Drug Administration (FDA). Until recently, orlistat, a pancreatic lipase inhibitor that blocks about one-third of daily fat absorption, was the only FDA-approved antiobesity drug available for long-term use in the United States and is still the only one approved for adolescent use. Many patients discontinue treatment with orlistat because of its unpleasant side effects of oily spotting, flatulence, and fecal urgency. Phentermine-topiramate (Qsymia® [formerly Qnexa®], Vivus, Inc., Mountain View, CA) provides a new option for patients who are obese and seeking medical therapy for weight loss.

Phentermine-topiramate is a controlled-release formulation of two separate FDA-approved drugs. This drug combination acts on the central nervous system as an appetite suppressant.[1] 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.[2,3] Topiramate is a gamma aminobutyric acid agonist that was approved by FDA in 1996 for treating epilepsy at a dose of approximately 400 mg/day and has been known to have weight loss as a side effect.[2,3] Topiramate was studied as a monotherapy for treating obesity; however, dose-dependent neuropsychiatric adverse events precluded further study.[2] By combining the effects of a low dose of each medication in a single treatment, phentermine-topiramate promotes 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.[1] Commercially, phentermine plus topiramate is available at four 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, a three-quarter titration dose of phentermine 11.25 mg plus topiramate 69 mg, and a high dose of phentermine 15 mg plus topiramate 92 mg.[4]

In 2011, Kushner and colleagues announced results from a phase III clinical trial (SEQUEL) evaluating the safety and efficacy of phentermine-topiramate in 675 patients with a body mass index (BMI) between 27 and 45 kg/m^2 and two or more obesity-associated comorbidities. This study is an extension of a phase III, clinical trial (CONQUER). Authors reported the following:[5,6]

> Patients treated with [Qsymia] had significant, sustained weight loss compared to those in the placebo group over two years. Average weight loss at week 108 was -9.3% and -10.5%, respectively, for the mid- and top-dose as compared to -1.8% for the placebo group (lease-squares mean ITT-LOCF [intention to treat–last observation carried forward]). [Qsymia] patients had improved cardiovascular and metabolic risk factors and a decrease in the need for associated medications in comparison with the placebo group. Placebo patients had a three times greater likelihood to progress to type 2 diabetes mellitus (T2DM) compared to subjects receiving top-dose [Qsymia] and a two times greater likelihood than patients on mid-dose [Qsymia].

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 patients who were morbidly obese. 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 ($p<0.00010$)."[7] The authors also reported that among patients who completed top-dose treatment of phentermine-topiramate, the following losses were observed:[7]

- 83.5% lost 5% or more of their baseline weight
- 67.7% lost 10% or more of their baseline weight
- 48.1% lost 15% or more of their baseline weight

Common adverse events reported in this study were paresthesia (tingling), dysgeusia (taste alteration), and xerostomia (dry mouth).[7]

FDA approved the drug on July 17, 2012, on the basis of two completed, phase III trials. The approved indication is as "an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 or greater (obese), or 27 or greater (overweight) in the presence of at least one weight-related comorbidity, such as hypertension, type 2 diabetes mellitus or high cholesterol (dyslipidemia)."[8] A Risk Evaluation and Mitigation Strategy (REMS) was required for Qsymia approval, informing prescribers and "female patients of reproductive potential" of potential risks with Qsymia use, including fetal orofacial cleft development during the first trimester of pregnancy, the need for pregnancy preventive practices for females of reproductive potential and immediate drug discontinuation in event of pregnancy.[8] Additionally, "Qsymia REMS program includes a Medication Guide, Healthcare Provider training, distribution through certified pharmacies, implementation system and a time table for assessments."[8] On September 17, 2012, this drug became commercially available in the United States.[9]

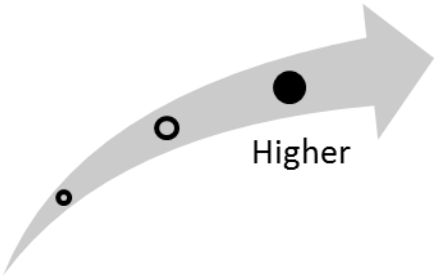
Patients' out-of-pocket costs for the drug are between about $120 and $185 per month.[4,10] Concerns exist regarding patient out-of-pocket expenses because of lack of reimbursement coverage by third-party payers or high patient copayments. Qsymia's diffusion expectations could also be quelled by physicians' ability to prescribe phentermine and topiramate separately and off-label to significantly mitigate patient out-of-pocket expenses.

Qsymia's main anticipated market competitor is lorcaserin (Belviq®), a 5-hydroxytryptamine type 2C (5-HT2C) receptor agonist that selectively stimulates the 5-HT2C serotonin receptors in the brain, which are involved in controlling appetite and metabolism.[11] FDA approved the drug on June 27, 2012, although this drug's commercialization has been delayed until early 2013 pending the U.S. Drug Enforcement Administration's review of FDA's recommendation to classify lorcaserin as a Schedule IV drug.[12]

Clinical Pathway at Point of This Intervention

Patients are usually evaluated for obesity in a primary care setting in which clinicians take height and weight measurements to calculate BMI. Individuals with a BMI $\geq$30 kg/m^2 are classified obese. Obese individuals are screened for other comorbid conditions, such as diabetes and hypothyroidism, that may influence treatment decisions and outcomes.[13] 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.[14,15] Patients with a BMI $\geq$30 kg/m^2 or a BMI $\geq$ 25 kg/m^2 with comorbid obesity-related risk factors or diseases (e.g., hypertension, dyslipidemia, coronary heart disease, T2DM, sleep apnea) may be candidates for drug therapy.[14,15] Drug therapy is typically offered in conjunction with a program of physical activity, nutrition counseling, and behavior management.[14]

Figure 1. Overall high-impact potential: phentermine-topiramate (Qsymia) for treatment of obesity



Experts commenting on this drug combination expressed optimism about its ability to meet the need of patients who are obese, given the lack of effective interventions for treating obesity. Experts generally indicated that both patient and clinician acceptance would be high for this intervention, because the potential to eliminate long-term sequelae of obesity is critically important. However, a potential increase in per-patient cost might serve as a barrier to acceptance by some patients. While preliminary results are promising, further studies evaluating efficacy and safety are needed, experts opined. Overall, experts agreed that antiobesity pharmacotherapies could serve as an effective alternative to current interventions for obesity. Based on this input, our overall assessment is that this intervention is in the high 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.[16-22]

The experts generally indicated that antiobesity drug therapy has a high potential to meet a significant unmet need in obesity treatment. One clinical expert commented, "There is a significant gap in obesity treatment care for those patients who do not qualify for bariatric surgery but still need help beyond lifestyle measures alone. Adjuvant medications are limited at present. Additional medications which are safe could help to fill this gap."[18]

Experts generally agreed that phentermine-topiramate has moderately high potential to significantly improve patient health outcomes, with one expert stating, "There have been a number of studies of [Qsymia] each of which shows a weight loss of between 5 and 15% from baseline. This seems quite significant."[19] Experts remained optimistic about preliminary trial results, although some would like to evaluate long-term, safety trial results before comprehensively assessing this drug's potential health outcomes. However, based on the results from these preliminary studies, experts believe phentermine-topiramate holds strong promise compared with previously and currently investigated antiobesity drugs.

Experts generally agreed that costs associated with antiobesity pharmacotherapies and potential third-party payers' unwillingness to cover these therapies might serve as barriers to reducing health disparities related to obesity. A majority of experts agreed the potential for an obesity drug intervention would not significantly disrupt the current health care delivery infrastructure. Several experts opined 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 an effective antiobesity medication is moderately high. While several experts mentioned the uncertainty of long-term adverse events as a potential barrier to patient acceptance of antiobesity pharmacotherapies, one expert opined that patients would acceptingly adopt "a pill, with minimal side effects, and a potential for a 10% weight loss."[19]

Several experts highlighted the fact that antiobesity pharmacotherapy is typically not covered by third-party payers and expected patients to have to bear the costs out of pocket. Although out-of-pocket expenses for phentermine-topiramate are estimated at $1,000–$2,000 per year, several experts believe the potential health outcomes far outweigh the financial costs, if a patient can afford the cost. A majority of experts thought that reducing or eliminating long-term complications from obesity might ultimately reduce per-patient costs over time. Several experts indicated that initial costs of using these pharmacotherapies might be lower than the cost of undergoing bariatric surgery or other antiobesity surgical interventions.

EndoBarrier Endoluminal Sleeve for Treatment of Obesity and/or Type 2 Diabetes

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

The 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. 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. 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. 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.[23] The device is intended to remain in place for 12–24 weeks, during which time the patient is on a liquid diet supplemented with multivitamins and proton pump inhibitors to control acid reflux.[23-25] 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.[23]

In 2012, Escalona and colleagues announced results from a 46-patient clinical trial (SEQUEL) evaluating weight loss sustainability and metabolic improvement following 2 years with EndoBarrier implantation. Authors reported the following:[26]

> Weight loss at one year in 27 subjects who completed the protocol was 22.8±16.4 kg, or 20.2 ±7.8% of total body weight ($p<0.001$). Weight loss in 8 subjects at one year post implantation and at 12 months post-explantation was 21.6 ±10.7 kg, or 16.1±9.2% ($p=0.005$) and 16.1±11.5 kg, or 14.4±9.2% of total body weight ($p=0.005$), respectively. Metabolic improvements included decreases in waist circumferences of 16.0 cm ($p=0.0006$) and LDL [low-density lipoprotein] cholesterol of 17.5 mg/dL ($p=0.001$)."

In one European-based trial, 30 patients with a mean BMI of 48.9 kg/m^2 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/m^2 who underwent dietary restriction alone. Researchers reported that implantation was successful in 26 of 30 patients; however, the device was removed from 4 patients after 12 weeks because of device migration, dislocation of the device anchor, sleeve obstruction, or continuous epigastric pain. 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 ($p<0.002$). Adverse events were reported in 100% of patients in this study. The majority were reported as abdominal pain and nausea during the first week after implantation; however, during the first week after implantation, 23% of patients were reported to have vomiting and after explantation, 50% of patients were reported to have pseudopolyp formation and 38.5% of patients were reported to have implant-site inflammation.[23]

In a second European trial, EndoBarrier implantation was attempted on 27 patients whose outcomes were compared with 29 patients who underwent a sham implantation. Researchers reported that of 21 patients in whom EndoBarrier was successfully implanted, 8 terminated treatment before the full 12-week treatment for the following reasons: GI bleeding (n=3), abdominal pain (n=2), nausea and vomiting (n=2), and an illness unrelated to treatment (n=1). Thirteen patients who received the EndoBarrier and 24 patients who underwent sham treatment completed the 12-week study with reported excess weight losses of 11.9% and 2.7% for the EndoBarrier and sham arms, respectively.[27]

Results from three trials were reported in a company press release on presentations given at the Second World Congress on Interventional Therapies for Type 2 Diabetes in March 2011, in Parkstad Heerlen, The Netherlands.[28] One trial was on EndoBarrier's effects on two hormones (gut peptides glucagon-like peptide-1 [GLP-1] and peptide YY [PYY]) and other diabetes measures. Jan Willem Greve, M.D., Ph.D., of the Gastrointestinal and Bariatric Surgery practice, Parkstad Heerlen, 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 of a study of 17 patients who were obese and had T2DM who received the 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 at 1 week after 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.[28]

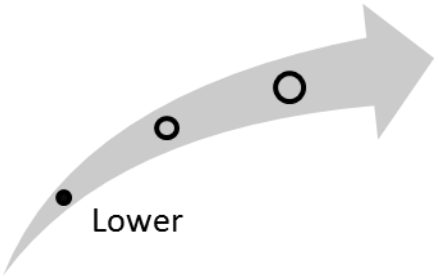
In a press release, the manufacturer cited as evidence results of two other clinical trials indicating that the EndoBarrier may be a candidate for the primary therapy of T2DM and obesity.[28] E.G. Moura, M.D., Ph.D., director of endoscopy, Hospital das Clinicas, University of São Paulo, Brazil, evaluated 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 1 year after implantation in 46 patients who were obese. 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%).

The EndoBarrier was Conformité Européene (CE) marked in 2009 for use in Europe. Results of two European-based trials of the EndoBarrier device were published in 2010,[23,27] and updated results from three studies were reported by the company in March 2011.[28] In July 2011, the system was approved by the Australian Therapeutic Goods Administration for inclusion in its therapeutic goods registry for treating T2DM and obesity for up to 12 months.[29] The company has not yet submitted a premarket approval application (PMA) to FDA, pending outcomes of ongoing investigational device exemption trials. In October 2012, FDA approved the company's request to begin a 25-site pivotal trial for this device for treating obesity and T2DM. The company believes trial results will support PMA submission for this device.[30]

Clinical Pathway at Point of This Intervention

The National Institutes of Health's Panel on Weight Loss recommended that patients who are morbidly obese lose 10% of their excess body weight before bariatric surgery to help reduce surgical risks and postoperative complications.[31] However, currently available preoperative weight loss methods have demonstrated suboptimal success in patients who are morbidly obese. Losing weight through diet and exercise alone has often not been successful in this patient population. Therefore, physicians may also recommend weight-loss medication.[31]Patients and clinicians would welcome the availability of other options for promoting preoperative weight loss in patients who have not lost weight using conservative treatment options.

Figure 2. Overall high-impact potential: EndoBarrier endoluminal sleeve for treatment of obesity and/or type 2 diabetes



Overall, experts commenting on this intervention thought that EndoBarrier appears to have potential to promote moderate, temporary weight loss, which could aid patients who are super-morbidly obese in achieving the required weight to undergo bariatric surgery and could also help improve diabetes-associated metabolic factors. The potential was tempered by experts' significant concerns about reported adverse events and termination of device use (explantation) by patients in trials. Experts 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.[32-37] Experts agreed that a significant unmet need exists for treatments that could aid patients who are morbidly obese in losing weight to become eligible for bariatric surgery or in reducing the risks associated with diabetes, citing the increasing prevalence of obesity in the United States and the current lack of effective noninvasive weight-loss treatments for this population. Additionally, 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 reported side effects and adverse events 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 the intervention 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 gastric 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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