

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

Priority Area 10: Obesity

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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. HHSA290-2010-00006-C). 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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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 Interventions 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.

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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 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are 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 a year. Topics eligible for inclusion are those interventions expected to be within 0–3 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 150 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 five to 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 high-impact-potential 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 or pivotal data for devices were available; (2) information was compiled and sent for expert comment before November 4, 2014, in this priority area; and (3) we received five to seven sets of comments from experts between January 1, 2014, and November 13, 2014. (Eight topics in this priority area were being tracked in the system as of November 4, 2014.) The three topics marked with asterisks emerged as having higher-impact potential on the basis of expert comments and assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by device and then, pharmaceuticals. 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. * Intra-gastric dual balloon (ReShape Duo) for treatment of obesity	Lower end of the high-impact-potential range
2. * Liraglutide (Saxenda) for treatment of obesity	Moderate
3. Naltrexone and bupropion extended-release (Contrave SR) for treatment of obesity	No high-impact potential; archived from horizon scanning system
4. * Vagus nerve blocking (Maestro system VBLOC) for treatment of obesity	Lower end of the high-impact-potential range

Discussion

According to a 2013 report from the National Center for Health Statistics, about 68% of American adults are overweight or obese (defined as an excess accumulation of body fat). Obesity was at one time thought to be simply the outcome of caloric intake that exceeded energy expenditure. However, researchers now know that other factors including genetics, metabolism, behavior, environment, culture, and socioeconomic status contribute to obesity. Obesity is associated with mortality and comorbidities including type 2 diabetes mellitus (T2DM), coronary artery disease, dyslipidemia, cardiometabolic syndrome, hypertension, stroke, sleep apnea,

osteoarthritis, gall bladder disease, and some cancers. In June 2013, the American Medical Association adopted a policy that recognizes obesity as a disease.

Body mass index (BMI) is a measure of an individual's weight relative to his or her height (kg/m^2). BMI is significantly correlated to an individual's body-fat percentage and is used as a measure to determine whether someone is overweight or obese. Patients with a BMI of 25 kg/m^2 or higher are considered to be overweight, and patients with a BMI of 30 kg/m^2 or higher are considered to be obese. Obesity is further classified as extreme or morbid in individuals with a BMI of 40 kg/m^2 or more.

Body fat distribution is also an important determinant of disease risk. Excess body fat in the abdominal area that is out of proportion to total body fat is known to be an independent predictor of morbidity and early mortality. Waist circumference positively correlates to the amount of abdominal fat, and it can be used clinically to assess disease risk in patients. A waist circumference of more than 37 inches in men and 31.5 inches in women is associated with increased cardiovascular risk. Because of even greater morbidity risk, therapeutic intervention is considered to be urgently needed in men with a waist circumference greater than 40 inches and in women with a waist circumference of more than 35 inches.

Worldwide, obesity rates have more than doubled since 1980. In 2008, more than 1.4 billion adults aged 20 years or older were overweight; 500 million people were obese.

In the United States, 34.9% of adults are obese. Among children and adolescents aged 2–19 years, 32.9 million are overweight or obese and 12.7 million are obese. Overweight adolescents have a 70% chance of becoming overweight adults. Non-Hispanic blacks have the highest age-adjusted rates of obesity (47.8% are obese), followed by rates for Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%). Non-Hispanic black and Mexican-American men with higher incomes are more likely to be obese than non-Hispanic black and Mexican-American men with low incomes. Low-income women are more likely to be obese than high-income women. Prevalence of obesity in adults has increased across all income and education levels. In children, obesity is higher among children living in low-income, low-education, and higher-unemployment households.

Finkelstein and colleagues (2009) estimated total annual U.S. medical costs associated with obesity to be \$147 billion and individual medical costs to be \$1,429 higher for obese people than for individuals of normal weight.

Only one surgical treatment (gastric bypass surgery) has definitively demonstrated long-term efficacy for patients who are morbidly obese. Until mid-2012, orlistat was the only U.S. Food and Drug Administration (FDA)-approved antiobesity pharmacotherapy available for long-term use in the United States. Surgery carries significant risks of morbidity and mortality, and drug therapy can have undesired side effects and limited efficacy in achieving sufficient weight loss. Additional treatment options are highly desired. Besides tracking new pharmaceutical options, we are tracking development of some devices. FDA held a public workshop Dec. 19-20, 2013, on obesity medical device innovation to address and discuss concerns about the regulatory pathway for new obesity devices. The outcomes of the meeting remain to be seen.

In September 2011, concerns over the lack of effective pharmacotherapies for treating obesity drove the U.S. Congressional Committee on Appropriations to direct FDA to develop a pathway, by March 30, 2012, to support antiobesity drug development. That prompted FDA to work more closely with manufacturers, eventually leading to the summer 2012 drug approvals phentermine-topiramate (Qsymia[®], Vivus, Inc., Mountain View, CA) and lorcaserin (Belviq[®], Arena Pharmaceuticals, Inc., San Diego, CA). In September 2014, FDA approved naltrexone-bupropion (Contrave[®], Orexigen Therapeutics, Inc., La Jolla, CA) for treating obesity. Additionally, liraglutide (Saxenda[®], Novo Nordisk a/s, Bagsvaerd, Denmark), FDA approved under the brand name

Victoza® for managing T2DM, has been used off label for treating obesity while the company pursues a labeled indication for treating obesity. This drug is injected. In October 2014, an FDA advisory committee recommended the drug for approval, and a decision is pending.

Devices in development for treating obesity include a temporary-placement gastric dual-balloon and a vagal nerve stimulator, each intended to offer a less invasive alternative to bariatric surgery. Experts commenting on these topics rated them differently, basing their opinions on the available data on efficacy and side effects.

Historically, pricing, reimbursement, and prescribing barriers have been the priority for the manufacturers of antiobesity pharmacotherapies to improve what has initially been slow diffusion and lower-than-projected sales. Liraglutide might face fewer accessibility issues because it is a recognized T2DM treatment and because it could simplify treatment for patients who are both diabetic and obese. The cost of liraglutide at the dosage used to treat obesity is expected to be much higher than the other three oral antiobesity drugs approved in the past 2 years.

Eligible Topic Not Deemed High Impact

- Naltrexone and bupropion extended-release (Contrave®) is an antiobesity medication consisting of two separate FDA-approved drugs; the drug combination acts on the central nervous system by regulating both appetite and reward pathways in the brain. Naltrexone is an opioid antagonist drug that was originally approved by FDA in 1984 for treating opioid addiction and approved in 1994 for treating alcohol dependence. Bupropion is a weak dopamine and norepinephrine reuptake inhibitor that FDA approved in 1985 for treating depression. Combining a low dose of each medication in a single treatment, naltrexone and bupropion extended-release promotes weight loss while avoiding side effects potentially caused by high doses of either drug. FDA approved the drug in September 2014, basing its decision on the results of multiple clinical trials that enrolled about 4,500 patients. Experts commenting on this topic indicated that acceptance and adoption of this intervention would be limited because other antiobesity pharmacotherapies are available. They expressed concerns over the potential for adverse events and contraindications. They saw no potential for high impact in terms of treating obesity. In light of experts' comments, this topic is being archived in the Healthcare Horizon Scanning System.

Antiobesity Devices

Intragastric Dual Balloon (ReShape Duo) for Treatment of Obesity

- **Key Facts:** Some patients who are super-morbidly obese (BMI of 50 kg/m² or more¹) are ineligible for gastric bypass surgery because of surgical risks and complications related to their weight; if they wish to have the surgery they are required to lose weight first to become eligible. The ReShape Duo® dual intragastric balloon device (ReShape Medical, Inc., San Clemente, CA) might offer a nonsurgical alternative to such patients and enable them to lose enough weight to become eligible for gastric bypass surgery. The manufacturer purports that by occupying space in the stomach, the dual intragastric balloon causes patients to reach satiety with less food intake. A clinician inserts ReShape Duo into the patient's stomach via an endoscope and guidewire. The uninflated balloons are advanced into the stomach with the guidewire and, once in the stomach, are inflated individually with equal volumes of saline. Device placement is a 15–30 minute outpatient procedure that requires only conscious sedation. The Reshape Duo is designed to be kept in the stomach for 6 months and then removed, using an endoscopic procedure similar to balloon placement. ReShape

Duo has been studied in a pivotal investigational device exemption (IDE) clinical trial of patients with BMIs between 30 and 40 kg/m². The company announced that it submitted a premarket approval application to FDA in July 2014; no date for a decision has been released and the device is not yet listed on an FDA advisory committee schedule for review. ReShape Duo has been Conformité Européene (CE) marked since 2007 and, after some product revisions, was launched in the United Kingdom in March 2012. In the United Kingdom, ReShape Duo and its associated procedure reportedly cost £4,450, an equivalent to \$7,000 at December 2014 exchange rates.

- **Key Expert Comments:** Overall, experts thought that ReShape Duo has potential to fulfill a large unmet need for patients who are obese and have unsuccessfully tried lifestyle and pharmacotherapeutic approaches to weight loss, who are ineligible for bariatric surgery, or both. Experts agreed on the potential of this intervention to improve patient health by promoting short-term weight loss. However, experts generally indicated a need for more trials to determine the safety and efficacy of ReShape Duo. Both patient and clinician acceptance has the potential to be high if the intervention proves to be safe and efficacious in the long term, experts commented. They anticipate a minimal impact on health care delivery processes because required infrastructure is widely available. Experts were unsure about the potential of this intervention to affect costs of care, because of a lack of long-term results.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Vagus Nerve Blocking (Maestro System VBLOC) for Treatment of Obesity

- **Key Facts:** The Maestro System VBLOC (EnteroMedics, Inc., St. Paul, MN) might offer an alternative to surgical weight loss procedures, such as gastric bypass, that permanently alter patient anatomy. The manufacturer purports that intermittent vagus nerve blocking (VNB) can both inhibit gastric motility and increase patient satiety, thereby inducing weight loss in obese patients. A clinician implants Maestro laparoscopically through five surgical access points. Device placement is a 60–90-minute procedure that requires general anesthesia. The device can be adjusted, activated, and deactivated noninvasively, and can entirely be removed, if needed. Maestro is being investigated in a pivotal IDE clinical trial of patients with BMIs between 40 and 45 kg/m² and patients with BMIs between 35 and 40 kg/m² with at least one obesity-related comorbidity. The company submitted a premarket approval application to FDA; in June 2014, the Gastroenterology and Urology Devices Panel of FDA's Medical Devices Advisory Committee voted to recommend that FDA grant EnteroMedics marketing approval for its Maestro RC system to treat obesity. FDA's decision is pending. Maestro has been CE marked since 2009 for treating obesity. In September 2014, the company announced that its CE mark had been expanded to include the management of T2DM. Although the device is not yet approved for marketing in the United States, one cost estimate lists laparoscopic implantation of the Maestro system at approximately \$20,000.
- **Key Expert Comments:** Overall, experts agreed that a moderate unmet need exists for effective treatment options for patients with obesity who are not candidates for bariatric surgery and have not successfully responded to available treatment strategies. Experts agreed on the potential of this intervention to improve patient health in the short term, but were uncertain regarding long-term safety and efficacy. Experts generally anticipated moderate acceptance by both patients and clinicians if the intervention proves to be safe and

efficacious in the long term. Health care delivery processes would be minimally impacted, experts commented, because the required infrastructure is widely available. Experts generally agreed that diffusion of this intervention could largely depend on the level of insurance coverage, and listed its substantial cost as a potential barrier.

- **High-Impact Potential:** Lower end of the high-impact-potential range

Antiobesity Drug

Liraglutide (Saxenda)

- **Key Facts:** Liraglutide (Saxenda) is a synthetic analog of the peptide hormone glucagon-like peptide-1 (GLP-1), which is recognized (Astrup et al., 2009) for its ability to suppress appetite and energy intake, as well as delay gastric emptying. The drug is believed to induce a feeling of satiety, which can result in less caloric intake and weight reduction. Liraglutide is engineered to have a substantially longer half-life than endogenous GLP-1 (13 hours, 1–2 minutes, respectively). Liraglutide is already approved as Victoza to treat T2DM, and, even though several oral antiobesity medications are now on the market, interest is high in liraglutide because it acts independently as a potential weight-loss treatment as well as being a T2DM treatment. Thus, for patients with T2DM who wish to lose weight, the drug might address both health issues at once. The drug is being used off-label for weight loss, according to a survey of primary care physicians published in January 2011. Liraglutide is under investigation for obesity treatment in a four-part, phase III clinical trial (SCALE). The drug is administered at a dosage of 3 mg daily in a 6 mg/mL, 3 mL FlexPen® for subcutaneous injection. The dosage used for T2DM is much lower (1.2 mg or 1.8 mg) than that proposed for obesity treatment (3 mg). As of December 2014, GoodRx, a U.S.-based online aggregator of prescription drug prices, reported prices ranging from about \$622 to \$651 for 1 carton (3 pens) of liraglutide 18 mg/3 mL. A generic formulation is not available. If priced similarly to the diabetes indication, this would provide 18, 3 mg doses—the daily dose for which the manufacturer is seeking FDA approval—at a cost of about \$35 to \$36 per dose. The yearly cost per patient would be about \$13,000 at current pricing. In September 2014, an FDA advisory panel recommended approval in a 14-1 vote.
- **Key Expert Comments:** Experts cited the need for safe and effective pharmacologic agents for treating obesity to be a significant unmet need. They noted the potential of this intervention to improve patient health by promoting weight loss and decreasing related comorbidities. Experts generally agreed that wide use of liraglutide could be limited by cost, gastrointestinal side effects, and long-term safety, which has yet to be established in this patient population. Some experts expressed concern over the need for patients to self-administer the drug using an injector pen; however, most experts agreed that patients would require minimal education. Still, the mode of administration could potentially deter patients from using liraglutide, most experts agreed. The cost of this intervention could be offset by the decrease in obesity-related complications, most experts noted, and they agreed that the prevalence of off-label liraglutide prescription indicates the potential for widespread adoption.
- **High-Impact Potential:** Moderate

Antiobesity Device Interventions

Intragastric Dual Balloon (ReShape Duo) for Treatment of Obesity

Unmet need: Bariatric surgery in the form of gastric bypass, sleeve gastrectomy, or laparoscopic banding, is considered to be effective in many patients for treating obesity; however, some of these procedures are very invasive with serious risks and side effects, and some permanently alter the anatomy. These procedures are indicated only for morbidly obese patients (body mass index [BMI] of more than 40 kg/m²) or for obese patients with BMIs of 35–40 kg/m² who have related comorbidities. However, morbidly obese patients who are at high surgical risk (e.g., unstable angina, acute heart failure) are typically precluded from such surgery. Therefore, minimally invasive treatments are needed that could enable these patients to lose weight and that could help super-obese patients who want to undergo bariatric surgery lose enough weight to be eligible for it, thereby reducing surgical risk.² The ReShape Duo[®] is a dual intragastric balloon implant being investigated for nonsurgical obesity treatment in patients with BMIs of 30 to 40 kg/m².

Intervention: Weight loss with the Reshape Duo is intended to be achieved by reducing the stomach's capacity: an inflated dual balloon occupies space in the stomach, purportedly causing the patient to achieve satiety with less food intake.³ Placement of the Reshape Duo is purportedly a 15–30 minute outpatient procedure requiring only conscious sedation. The clinician delivers the dual intragastric balloons to the patient's stomach through the patient's mouth via an endoscope and guidewire. The uninflated balloons are advanced into the stomach with the guidewire; once in the stomach, the balloons are inflated individually with equal volumes of saline totaling 900 cc, or 450 cc for each balloon.^{3,4} Compared to single intragastric balloons, which are inflated with 400–700 cc of saline, the dual-balloon design of Reshape Duo purportedly allows for a greater stomach volume to be occupied without overdistention.³ The company states that the dual balloon is also designed to conform with the stomach's natural curvature and reduce the risk of balloon migration and obstruction that is seen with single intragastric balloons.³

The Reshape Duo is designed to be kept in the stomach for no longer than 6 months. After that time, clinicians remove the balloons using an endoscopic procedure similar to the balloon placement. During this procedure, a clinician places the endoscope in the patient's stomach while the patient is under conscious sedation. The endoscope is fitted with a "proprietary suction cap" to drain the saline from the balloons individually in a controlled manner. Once the balloons are drained, the clinician secures the deflated dual balloon's tip with a snare on the endoscope and removes the device through the patient's mouth.⁴

In a pivotal clinical trial conducted for the premarket approval application, the ReShape Duo was tested in patients with BMIs of between 30 and 40 kg/m².⁵

Clinical trials: In 2013, Ponce and colleagues reported results of a randomized controlled trial (RCT) of 30 patients who were assigned in a 2:1 ratio to receive the balloon or medically supervised lifestyle changes as a control group. They reported that after 24 weeks, the mean excess weight loss in the Duo balloon group was 31.8%±21.3% and in the control group was 18.3%±20.9% (p=0.1371). Weight loss in pounds or kilograms was not reported.⁶ The authors reported that at 48 weeks, which was 24 weeks after device removal, patients treated with ReShape Duo had maintained 64% of their weight loss.⁶ The authors reported that no deaths, unexpected adverse events (AEs), or balloon deflations or migrations occurred. Severe nausea caused four patients to be admitted to the hospital for treatment; two patients had minor events during balloon removal at 24 weeks.

In November 2014, a manufacturer's press release announced results from the pivotal RCT (REDUCE) that enrolled 326 patients at eight participating sites.^{7,8} The RCT assessed the safety and effectiveness of ReShape Duo combined with lifestyle modification in patients with BMIs of 30–40 kg/m² compared with results of lifestyle and dietary modifications alone.⁷ The authors reported that at 24 weeks, 55% of patients treated with Reshape Duo lost at least 25% of their excess weight.⁷ Authors also reported that no balloon migrations or obstructions occurred.

Manufacturer and regulatory status: ReShape Duo is being developed by ReShape Medical, Inc. (San Clemente, CA). The device has been Conformité Européene (CE) marked since 2007, allowing marketing in Europe; after product revisions, it was launched in the United Kingdom in March 2012.⁹ The company announced that it submitted a premarket approval application to the U.S. Food and Drug Administration (FDA) in July 2014 after the pivotal trial met its primary efficacy endpoints.^{10,11} No date has been announced for an FDA decision, and the device does not yet appear on an FDA advisory committee schedule for review.

Diffusion and costs: If ReShape Duo is approved for treating obesity and third-party coverage and reimbursement become available, moderate diffusion is expected as an adjunct to lifestyle modifications. Another intragastric balloon (Garren-Edwards gastric bubble) was withdrawn from the U.S. market because of concerns about safety and efficacy, which might negatively affect how patients and clinicians view ReShape Duo.¹² In 1987, the U.S. Centers for Medicare & Medicaid Services established a national coverage determination (NCD) regarding gastric balloons. The NCD indicated that “the use of the gastric balloon is not covered under Medicare, since the long term safety and efficacy of the device in the treatment of obesity has not been established.”¹³

Because of this NCD, intragastric balloons coming to the U.S. market would have to undergo a new formal national coverage analysis to establish coverage under Medicare; if Medicare covered the balloons, other third-party payers might follow suit. The cost of the ReShape Duo device and implantation procedure is expected to range between \$7,000 and \$8,000, which might make it more appealing than surgical procedures for some patients.^{14,15} However, diffusion is likely to be hampered if payers choose not to reimburse for its use.

For patients with BMIs between 30 and 40 kg/m², ReShape Duo could compete with recently approved pharmacotherapies for obesity (e.g., Qsymia®, Belviq®, Contrave®).¹⁶ Weight-loss surgery is indicated for patients only after other therapies have failed or in cases in which patients are experiencing complications related to their obesity.¹⁷ Therefore, ReShape Duo will likely compete with these surgeries only in patients with BMIs of 35 kg/m² or more and obesity-related comorbidities. ReShape Duo also could complement weight-loss surgeries in some patients. Bariatric surgery in patients with BMIs higher than 40 kg/m² can present high surgical risk and technical challenges, and these patients may benefit from preoperative weight loss.¹⁸ If the indications for ReShape Duo include patients with BMIs this high, the device could serve as a noninvasive means for weight loss before bariatric surgery.

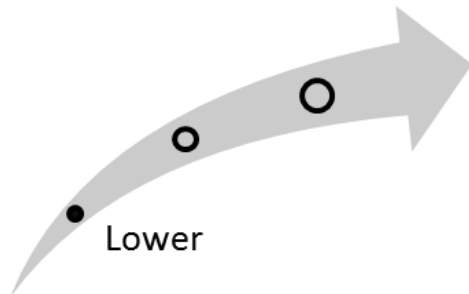
ReShape Duo may also compete with other minimally invasive endoluminal treatments that are in development, such as the EndoBarrier® endoluminal sleeve and vagus nerve blocking.¹⁹

Clinical Pathway at Point of This Intervention

The National Heart, Lung and Blood Institute's Panel on Weight Loss recommends that patients who are morbidly obese lose 10% of their excess body weight before bariatric surgery to help reduce surgical risks and postoperative complications.²⁰ Losing weight through diet and exercise alone has often been unsuccessful in this patient population. Therefore, physicians may also recommend weight-loss medication.²⁰ If goals are not achieved with medications, patients may opt for new, minimally invasive options (in development), such as intragastric balloons, including the

one discussed here, or vagus nerve block, also addressed in this report, should they become available in the United States.

Figure 1. Overall high-impact potential: intragastric dual balloon (ReShape Duo) for treatment of obesity



The expert comments for this topic were received before the November 2014 results reported from the pivotal clinical trial. Overall, experts commenting on this intervention agreed that ReShape Duo aims to fulfill a large unmet need for treatments for patients who are obese, have exhausted other weight-loss methods (e.g., medical therapy, behavior therapy), and are ineligible for bariatric surgery. However, experts agreed that available data available at the time they provided their comments were insufficient to determine whether ReShape Duo is safe and effective. One expert with a research perspective noted the success of behavior therapy programs compared with device implantation, which dampened her expectations for the intervention. This expert commented that patients who underwent behavior therapy achieved significant weight loss without the need for device implantation. A clinical expert also highlighted that a gap exists between those who are eligible for the device and those who actually receive it, with some patients declining because of safety concerns. This expert also noted that larger and long-term studies are needed to evaluate the safety and efficacy of this intervention. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems and administration backgrounds, provided perspectives on this topic.²¹⁻²⁶ These comments were received before the release in November 2014 of results of the 326-patient pivotal clinical trial.⁷ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Treating obesity remains a major health care challenge, the experts agreed, noting that few effective interventions are available for patients with the condition. ReShape Duo has potential to improve patient health, the experts generally agreed. However, some experts expressed concern regarding long-term efficacy and the potential for patients to regain weight after device removal. One clinical expert commented, “Given the duration of implantation and likelihood of weight regain, any short term gains will likely be neutralized after the device is removed.”²⁶ Most experts agreed that this intervention could provide a nonsurgical option for patients who do not wish to undergo bariatric surgery. Alternatively, it could be used as an initial weight-loss intervention for patients not yet qualified for surgery, some experts commented. However, some experts noted that available data showed no statistically significant improvement in outcomes for patients receiving gastric balloons compared with patients who underwent behavioral therapy alone. One expert with a research perspective commented, “Results from the only available study are not convincing; average weight loss was 30% for those with the balloons and 20% for those with behavioral therapy.”²⁵

Acceptance and adoption: Clinicians and patients are likely to accept the ReShape Duo if it demonstrates safety and efficacy in clinical trials, the experts thought. Most experts agreed that clinicians and patients would be willing to try an outpatient procedure that is less invasive than bariatric surgery. Expanding on this, one expert with a clinical perspective commented, “Clinicians are likely to accept this treatment because current medical interventions are not effective, and most patients do not want bariatric surgery.”²⁴ This expert also noted that patients would accept this intervention for similar reasons, but mentioned long-term safety as a concern. Overall, experts anticipated moderate acceptance due to the lack of effective medical interventions for treating patients who are obese.

Diffusion could largely depend on the level of insurance coverage, some experts opined. For instance, one expert with a clinical perspective commented, “It has the potential to be another tool in the toolbox. If not covered by insurance, uptake will be minimal. If covered by insurance, uptake will be greater....”²⁶

Health care delivery infrastructure and patient management: Use of this intervention is likely to have a minimal impact on health care delivery and infrastructure, the experts agreed. Most experts commented that device implantation can be performed in existing endoscopy or outpatient surgical suites. One expert with a clinical perspective commented, “This [balloon implantation] can be done routinely by gastroenterologists or surgeons in clinics, healthcare centers and hospitals.”²⁴ This expert also commented that infrastructure may need to be expanded because of the large number of patients eligible to be treated with this intervention.

The potential effect of this intervention on patient management is not clear, thought the experts. Minor disruption might occur because of the need for monitoring safety and the eventual device removal. One research expert thought moderate disruption could occur to patient management²² and another research expert commented, “The balloon is intended to be temporary, would require a placement and removal procedure, and if a significant number of patients sought treatment, would change the way obese/overweight patients are managed.”²⁵

Health disparities: Patient access to this intervention could be limited in people lacking third-party coverage for obesity interventions and unable to afford the device and procedure cost, most experts agreed. For example, one expert with a research perspective commented, “With the cost shown in other countries to be over 7,000 dollars it will create health disparities especially for people with no insurance or no coverage with Medicare services.”²¹ But another research expert opined that this intervention would have a minor impact on health disparities if used in place of pharmacotherapy. This expert anticipated that underserved populations would experience barriers to care similar to those of available treatment options.²²

Vagus Nerve Blocking (Maestro System VBLOC) for Treatment of Obesity

Unmet need: Obesity-related comorbidities such as hypertension, stroke, type 2 diabetes (T2DM), and heart disease are leading causes of preventable death in the United States; therefore, treatment strategies for weight loss in obese patients have become increasingly important in reducing morbidity and mortality.^{27,28} Bariatric surgery in the form of gastric bypass, sleeve gastrectomy, or laparoscopic banding, is considered to be effective in many patients for treating obesity; however, some of these procedures are very invasive with serious risks and side effects, and some procedures permanently alter the anatomy. These procedures are indicated only for morbidly obese patients (BMI of more than 40 kg/m²) or for obese patients with BMIs of 35–40 kg/m² who have related comorbidities. However, morbidly obese patients who are at high surgical risk (e.g., unstable angina, acute heart failure) are typically precluded from such surgery. Therefore, less invasive treatments are needed that could enable these patients to lose weight and that could help super-obese patients who want to undergo bariatric surgery lose enough weight to be eligible for it, thereby reducing surgical risk.² Intra-abdominal vagus nerve blocking (VNB) with the Maestro[®] system is intended to offer a safer, less invasive alternative to surgical weight loss procedures that may permanently alter patient anatomy.

Intervention: Intra-abdominal VNB uses high-frequency, low-energy electrical pulses to block vagus nerve signals in the abdominal region, inhibiting gastric motility and increasing satiety.²⁹ The Maestro system is intended to induce weight loss in adult patients with obesity. The proposed indication includes patients with BMIs of at least 40 kg/m² or greater than 35 kg/m² with one or more obesity-related comorbidities, who have failed at least one supervised weight-management program within the past 5 years.^{30,31} Maestro comprises a subcutaneously implanted neuromodulation device with two internal electrodes (placed on the anterior and posterior intra-abdominal vagal nerve trunks) and an external battery-powered controller. Surgeons implant the device and electrodes laparoscopically through five surgical access points. Patients are placed under general anesthesia during the 60–90 minute procedure.^{31,32}

This neuromodulation device consists of an integrated coil that acts as an antenna for telemetry and recharging. A rechargeable lithium ion battery with an estimated 8-year life is also housed inside the sterile, hermetically sealed case enclosure. It is implanted under the skin on the thoracic sidewall between 2 and 3 cm below the skin. The surgeon then programs the device with the external unit, a commercially available laptop computer equipped with proprietary software.^{30,31} Physicians use accompanying customized software on a standard laptop computer to establish a connection between the device's internal and external units. The software can also be used to retrieve diagnostic information and modify treatment parameters.³⁰

Surgeons can adjust, activate, and deactivate the device noninvasively and can entirely remove it if needed.²⁹ The system also includes an external, mobile charger that the patient can wear to recharge the device. It can also be charged with a standard, external alternating current (AC) charger.³¹ With the use of a transmitter coil, battery charging and device programming information is delivered transcutaneously (through the skin) via radiofrequency waves up to a maximum of 5 cm.³⁰⁻³² VNB therapy cannot be administered while the device is recharging.³¹

Therapy is delivered during the patient's waking hours.³² Electrical impulses are sent intermittently through the implanted electrodes to block vagus nerve signals. Intermittent blocking purportedly reduces potential adverse effects associated with permanent nerve resection. VNB may also reduce digestive enzyme secretion, thus reducing the amount of absorbed calories.^{29,30} In the pivotal trial, the device was programmed to deliver blocking therapy for 13 hours per day. Patients were required to perform daily battery checks and recharge as needed.³⁰

Clinical trials: In 2014, Ikramuddin and colleagues announced 12-month results of a long-term ongoing clinical trial evaluating the safety and effectiveness of intermittent VNB therapy for patients with BMIs of 40–45 kg/m² or 35–40 kg/m² with at least one obesity-related comorbidity. The study randomly assigned 239 patients to an active vagal nerve block device (162 patients) or a sham device (77 patients). All patients received weight management education. The authors reported that the vagal nerve block group achieved a mean 24.4% excess weight loss (9.2% of total body weight loss) versus 15.9% excess weight loss (6.0% total body weight loss) in the sham group. The mean difference in the percentage of excess weight loss between groups was 8.5 percentage points (95% confidence interval [CI], 3.1 to 13.9), which did not meet the 10-point target, although weight loss was statistically greater in the vagal nerve block group according to a post hoc analysis.³³ Study authors also reported that device, procedure, or therapy-related serious AEs in the vagal nerve block group occurred in 3.7% (95% CI, 1.4% to 7.9%) and was lower than the 15% event rate goal. The AEs that occurred more often in the vagal nerve block group were heartburn or dyspepsia and abdominal pain attributed to therapy; all were reported as mild or moderate in severity.³³

Manufacturer and regulatory status: The Maestro system is being developed by EnteroMedics, Inc. (St. Paul, MN). FDA granted the company an investigational device exemption in October 2010 to conduct clinical trials of its next-generation Maestro RC system for treating obesity. The company submitted a premarket approval application to FDA in June 2013.³¹ In June 2014, the Gastroenterology and Urology Devices Panel of FDA’s Medical Devices Advisory Committee voted to recommend that FDA grant EnteroMedics marketing approval for its Maestro RC system to treat obesity. The panel voted 8-1 in favor that the device is safe when used as designed and 4-5 against on the issue of a reasonable assurance of efficacy. The panel also voted 6-2 in favor that the device’s benefits outweighed the risks.³⁴ The manufacturer anticipated approval in 2014 and plans to enroll patients in a long-term, postmarket clinical trial.^{31,35}

Overseas, the company received Conformité Européenne (CE) mark approval in March 2009 to market the Maestro system in the European Union for treating obesity.³⁶ In July 2011, the company received CE mark approval to market the Maestro RC in the EU.³¹ In September 2014, the company announced that its CE mark for the Maestro RC had been expanded to include “the management of [T2DM] through improved glycemic control.”³⁷

Diffusion and costs: EnteroMedics has not announced device costs or estimated procedure costs. However, one estimate lists laparoscopic implantation of the Maestro system at approximately \$20,000.³⁸ As a proxy, we identified from ECRI Institute’s PriceGuide database the average cost for a vagus nerve stimulation device approved for treating refractory epilepsy and treatment-resistant depression to be \$20,000.³⁹ This does not include the implantation cost.

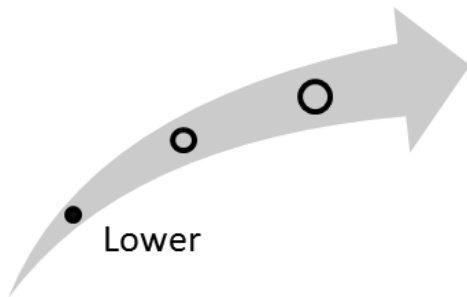
Most third-party payers consider vagus nerve stimulation to be investigational or experimental for treating obesity and therefore deny coverage. Payers that deny coverage include Anthem,⁴⁰ Blue Cross Blue Shield of Massachusetts,⁴¹ CIGNA,⁴² HealthPartners,⁴³ Humana,⁴⁴ Regence,⁴⁵ UnitedHealthcare,⁴⁶ and Wellmark.⁴⁷ If VNB is approved for marketing, it will likely have to demonstrate the potential to induce safe and effective weight-loss comparable to other minimally invasive weight-loss options for third-party payers to provide coverage.

Clinical Pathway at Point of This Intervention

The National Heart, Lung and Blood Institute’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.²⁰ Losing weight through diet and exercise alone has often been unsuccessful in this patient population. Therefore, physicians may

also recommend weight-loss medication, and several options are now available.²⁰ If goals are not achieved with medications, patients may opt for new, minimally invasive options in development, such as the VNB discussed here and intragastric balloons including the ReShape Duo covered in this report, should they become available in the United States market.

Figure 2. Overall high-impact potential: vagus nerve blocking (Maestro system VBLOC) for treatment of obesity



Overall, experts commenting on this intervention agreed that Maestro has the potential to fulfill a significant unmet need for treatments for patients who are obese, have exhausted other weight-loss methods (e.g., medical therapy, behavior therapy), and are ineligible for bariatric surgery. Some experts noted the potential for this intervention to be used as an alternative for obese patients required to lose weight before becoming eligible for bariatric surgery. However, several experts commented that available data are insufficient to determine whether Maestro is safe and effective. One expert with a research perspective noted the limited amount of long-term safety and efficacy data, which dampened his expectations for the intervention. A clinical expert also highlighted the lack of data regarding absolute weight loss and noted the need for specific safety concerns to be addressed, including the blood pressure drop observed in some patients with a Maestro implant. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Five experts, with clinical, research, health administration backgrounds, provided perspectives on this topic.⁴⁸⁻⁵² We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Treating obesity remains a major health care challenge, the experts agreed, noting that few effective interventions are available for patients with the condition. Additional therapy options are needed for patients with obesity who are not candidates for bariatric surgery or who do not wish to undergo invasive procedures that may permanently alter their anatomy. Maestro has the potential to improve patient health, the experts generally agreed. However, some experts expressed concern regarding long-term safety and efficacy and the potential for patients to regain weight when treatment has been discontinued. One research expert commented, “Will vagus nerve stimulation continue to provide weight loss benefit after several years of use? The nervous system may have compensatory mechanisms that circumvent vagus nerve block and restore baseline gut motility and enzyme secretion.”⁵² Most experts agreed that this intervention could provide a less invasive option for patients with obesity and could potentially be used as a bridge to certain bariatric surgeries. One research expert opined, “The only other option for this patient population is bariatric surgery which is invasive and alters anatomy. Also, some morbidly obese patients need an option to lose weight so they can become candidates for bariatric surgery.”⁴⁹

Acceptance and adoption: Clinicians and patients are likely to accept Maestro if it demonstrates safety and efficacy in further clinical trials, the experts thought. Most experts agreed that clinicians and patients would be willing to accept a less invasive procedure than bariatric surgeries that may alter anatomy. However, most experts agreed that this intervention would be a less attractive alternative compared to oral pharmacotherapy. One expert with a clinical perspective commented, “The device may seem less invasive to patients than classic bariatric surgery. It is going to be less attractive than pharmacotherapy but more attractive than some of the other surgical weight loss techniques.”⁵⁰ However, another expert representing a research perspective opined, “With the marginal success rate from early studies and the need to learn a new potentially complex implantation procedure, I think there might be some resistance (at least at first) by clinicians to adopt the VBLOC.”⁴⁸ Overall, experts anticipated moderate acceptance due to the lack of effective medical interventions for treating patients who are obese.

Diffusion could largely depend on the level of insurance coverage, some experts opined. One expert with a research perspective commented, “Most individuals would need third party payers to cover the cost of the device and surgical installation, the costs of which are considerable. Given that this technology is currently considered experimental by most, if not all, payers, the cost of the device and installation would need to be covered by the patient.”⁵⁰

Health care delivery infrastructure and patient management: Implementation of this intervention is likely to have a minimal impact on health care delivery and infrastructure, the experts agreed. Most experts commented that device implantation could be performed in existing outpatient surgical suites. One expert with a clinical perspective commented, “Since the surgery is laparoscopically performed, it can likely be performed on an outpatient basis. It should not require further investment in infrastructure or personnel.”⁵⁰ However, one expert representing a research perspective listed some factors that could impact health care delivery infrastructure, “Surgeons must be trained in implant procedure and centers performing the procedure must be certified. Each certified center must provide a patient follow-up program with diet and lifestyle modification plans, including enrollment in a support group.”⁴⁹

The potential effect of this intervention on patient management would be minimal, thought the experts. Most generally agreed that patients would be managed similarly to those who have undergone certain bariatric surgeries. One expert representing a health administration background commented, “Patient management would be very similar to that of gastric bypass and would have a minimal impact as a result.”⁵¹ However, one clinical expert anticipated potential minor disruptions related to device monitoring and adjustment. This same expert commented, “This may require more follow up time post-operatively than other weight loss procedures and surgeons will need to adjust their post-operative practices accordingly.”⁵⁰

Health disparities: Patient access to this intervention could be limited if patients have to pay out of pocket for this device because of lack of coverage and reimbursement. For example, one clinical expert commented, “Given that the device is not covered by insurance and that obesity mainly affects minorities this will affect health disparities as essentially only people who can afford to pay for the device will be able to obtain it.”⁵⁰ Another expert representing a health administration perspective opined, “Unless the costs are substantially subsidized by public payers (Medicare and Medicaid), many of the target population may not have access to the intervention which could subsequently contribute to an increase in disparities and access to care.”⁵¹

Antiobesity Drug Interventions

Liraglutide (Saxenda) for Treatment of Obesity

Unmet need: The increasing prevalence of overweight and obese populations in the United States has generated a need for novel pharmacologic therapies aimed at weight reduction when diet and exercise have failed. However, concerns over potential AEs associated with antiobesity pharmacotherapies significantly elevated FDA's regulatory bar for gaining approval and providing long-term safety data with new drug applications and committing to long-term postmarket studies.^{28,53} Until mid-2012, 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 remains the only one approved for adolescent use. Since then, three other drugs, phentermine/topiramate (Qsymia), lorcaserin (Belviq), and naltrexone/bupropion (Contrave), have been FDA approved. Liraglutide (Saxenda®), which has been recommended by an FDA advisory panel for approval, would provide another option for patients who are obese and seeking medical therapy for weight loss. Because the drug is already approved to treat T2DM, it could provide an option for obese patients who also have T2DM.

Intervention: Liraglutide is a synthetic analog of the peptide hormone glucagon-like peptide-1 (GLP-1) that has been shown to suppress appetite and energy intake and delay gastric emptying, which may induce a feeling of satiety.⁵⁴ The drug is FDA approved under the brand name Victoza® for managing blood glucose levels in patients with T2DM.⁵⁵ GLP-1 is a naturally occurring incretin hormone that stimulates insulin production in the presence of hyperglycemia and blocks the effects of glucagon, a hormone produced in the pancreas that signals the liver to release stored sugar into the bloodstream.⁵⁶

Endogenous human GLP-1 has a short half-life (1–2 minutes); however, liraglutide has been modified to allow binding to serum albumin, which increases its half-life to about 13 hours. It has been demonstrated to help blood glucose control by stimulating insulin release and lowering glucagon secretion in response to high glucose levels.⁵⁴

As an antiobesity treatment, liraglutide is self-administered once daily via subcutaneous injection using an automatic injection pen in daily doses ranging from 1.2 to 3.0 mg.⁵⁴ The dose range for treating T2DM is narrower—1.2 to 1.8 mg liraglutide daily. Thus, the dosage for treating obesity may be twice as high in some cases.⁵⁷ In practice, given that many patients with diabetes are also obese, the drug fulfills a dual role of managing both diabetes and obesity. Nonetheless, the manufacturer is pursuing a labeled indication for treating overweight and obesity.

Clinical trials: A four-part, phase III RCT, SCALE™ (Satiety and Clinical Adiposity-Liraglutide Evidence in Non-Diabetic and Diabetic people) is ongoing.⁵⁵ The trial includes more than 5,000 patients who are either overweight (BMIs of 27 kg/m² or more) with comorbidities (e.g., hypertension, dyslipidemia, T2DM) or obese (BMIs of 30 kg/m² or more).

In the first SCALE trial (SCALE™ Maintenance), 422 patients were pretreated with a 4- to 12-week, low-calorie diet, then randomly assigned to receive either liraglutide 3 mg daily administered in a 6 mg/mL, 3 mL FlexPen® for subcutaneous injection or placebo 3 mL daily FlexPen for subcutaneous injection. The authors⁵⁸ reported that the average initial weight loss for all individuals who were randomly assigned was 6.0% (6.3 kg). After 56 weeks of treatment, patients taking the drug had statistically significant improvements in all measures of weight loss compared with placebo ($p < 0.0001$ in all analyses). The liraglutide group had a net weight change of -6.1% versus 0.1% (-5.7 kg vs. 0.2 kg) in the placebo group. Significantly more liraglutide than placebo recipients maintained initial weight loss and continued losing more weight over time. More than twice as many participants on liraglutide lost more than 5% additional weight as did patients treated with placebo. Completion rates, serious AEs and withdrawals due to AEs were similar for each group. Nausea and vomiting were reported in more liraglutide than placebo group patients,

occurring mainly during dose escalation; 64% of liraglutide nausea cases were mild, and most cases declined in frequency by 4–6 weeks. Psychiatric AE rates were similar in each arm (11% and 12%).

The second trial of the series (SCALE™ Diabetes) was a double-blind RCT of 846 overweight or obese patients with T2DM who were randomly assigned in a 2:1:1 ratio to receive 3 mg liraglutide, 1.8 mg liraglutide, or placebo. After 56 weeks, patients discontinued treatment and were observed for an additional 12 weeks.⁵⁵ A company press release reported results regarding weight-loss. The patient population had a mean baseline weight of about 106 kg and BMI of 37 kg/m².⁵⁵ The liraglutide 3 mg and liraglutide 1.8 mg groups achieved 6% and 5% weight lost at 56 weeks, respectively, compared with a 2% weight loss for the placebo group. About 50% of patients achieved a weight loss of 5% and 22% achieved a weight loss of 10% after taking liraglutide 3 mg. In the 1.8 mg group, 35% achieved a 5% weight loss and 13% achieved a 10% weight loss. In the placebo groups, 13% achieved a 5% weight loss and 4% achieved a 10% weight loss. All differences for both doses of liraglutide were statistically significantly different from placebo, and the trial met all three co-primary endpoints. During the 12-week followup period after discontinuing treatment, people in both liraglutide groups regained some of the weight. Liraglutide was generally well tolerated, and the 56-week completion rate for liraglutide 3 mg, liraglutide 1.8 mg, and placebo was 77%, 78%, and 66%, respectively. Withdrawals due to AEs were below 10% in all treatment groups. In line with earlier liraglutide trials, the most common AEs were related to the gastrointestinal system and diminished over time. No other apparent differences between the treatment groups were observed with respect to AEs and standard safety parameters.

The third trial (SCALE™ Obesity and Prediabetes) was a 56-week, double-blind RCT evaluating liraglutide's potential to induce and maintain weight loss in nondiabetic patients. Investigators randomly assigned 3,731 patients who were overweight or obese (mean baseline weight of 106 kg and BMI of 38 kg/m²) in a 2:1 ratio to receive treatment with 3 mg liraglutide daily or placebo, in combination with diet and exercise.⁵⁹ A company press release reported preliminary results.⁵⁹ The average weight loss for the liraglutide group was 8.0% compared with 2.6% for the placebo group. In the liraglutide group, 64% achieved a 5% weight loss compared with 27% in the placebo group. In the liraglutide group, 33% achieved weight loss of at least 10% compared with 10% in the placebo group. All differences between liraglutide and placebo groups were statistically significantly different, and the trial met all three co-primary endpoints. Of all people participating in the trial, 61% had prediabetes when randomly assigned to a group. Sixty-nine percent of the 3 mg liraglutide group showed no signs of prediabetes at 56 week followup compared with 33% of the placebo group. The 56-week completion rate for liraglutide 3 mg and placebo groups was 72% and 64%, respectively. Withdrawals due to AEs were less than 10% in both groups. The most common AEs were related to the gastrointestinal system, and they diminished over time.

In November 2014, the manufacturer's press release announced further results from the SCALE™ Obesity and Prediabetes trial.⁶⁰ The press release reported that obese adults taking 3 mg liraglutide daily in combination with a reduced-calorie diet and physical activity achieved similar weight loss by 56 weeks, across a range of baseline BMI subgroups from overweight to class III obesity (BMI of 40 kg/m² or more). Adults given 3 mg liraglutide reported weight loss of 9.2% compared with 3.5% in the placebo group (estimated difference 5.7%, $p < 0.0001$). Patients in the active treatment group also reported improved health-related quality of life.

The fourth trial (SCALE™ Sleep Apnea; $n=340$) was a safety and efficacy trial investigating once-daily 3 mg liraglutide in combination with diet and exercise for reducing the severity of obstructive sleep apnea; however, data are not yet available.⁵⁹

Manufacturer and regulatory status: According to the manufacturer, Novo Nordisk a/s (Bagsvaerd, Denmark), liraglutide “is not approved for weight management and should not be prescribed for its treatment;” however, results from a 2011 survey (discussed below) suggest

widespread off-label use of the drug for treating obesity.^{55,61} Liraglutide is FDA approved (as Victoza) for managing blood glucose levels in patients with T2DM.⁵⁵ In December 2013, the manufacturer submitted a new drug application to FDA for liraglutide (3 mg dose),⁵⁷ and in September 2014, an FDA advisory panel recommended approval in a 14-1 vote. The manufacturer has indicated that the favorable panel recommendation supports labeling for “chronic weight management in individuals with a body mass index (BMI) 30 kg/m² or greater, or 27 kg/m² or greater in the presence of at least one weight-related comorbidity.”⁶² Thus, the drug will likely be used by patients with T2DM who need to lose weight. An FDA decision is expected in early 2015.

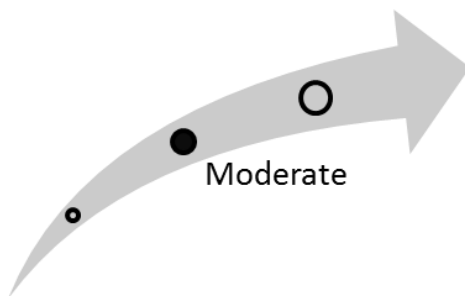
Diffusion and costs: A survey of primary care physicians published in January 2011 suggests that liraglutide and a second GLP-1 analog approved to treat T2DM, exenatide (Byetta®), are already being used off label to treat obesity. About one-third of surveyed primary care physicians listed one of these GLP-1 analogs as the obesity drug they perceive as being most efficacious.⁶¹ The dosage approved by FDA for diabetes is much lower than that intended for obesity treatment: the T2DM labeled dosage is for 1.2 or 1.8 mg as a once-daily injection.⁵⁷ As of December 2014, GoodRx, an online aggregator of prescription drug prices, reported prices ranging from about \$622 to \$651 for one 3-pen carton of liraglutide 18 mg/3 mL. If pricing is similar for the obesity indication, such a carton would provide 18 doses at the 3 mg dose (about \$35 to \$36 per dose) for which the manufacturer is seeking FDA approval.

Many third-party payers do not cover antiobesity medications, although health plans for federal employees are required to cover antiobesity medications. Payers for nonfederal beneficiaries who cover antiobesity drugs typically require that a patient has a comorbid condition (e.g., hypertension, T2DM). For liraglutide, at least one third-party payer (Aetna) considers weight-loss pharmacotherapy medically necessary in patients being treated in clinical trials.⁶³

Clinical Pathway at Point of This Intervention

Individuals who are obese are screened for other comorbid conditions, such as diabetes, heart disease, and hypothyroidism, which may influence treatment decisions and outcomes.⁶⁴ 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 weight gain.⁶⁵ Patients with BMIs of 30 kg/m² or more or BMIs of 25 kg/m² or more with comorbid obesity-related risk factors or diseases (e.g., hypertension, dyslipidemia, coronary artery disease, T2DM, sleep apnea) may be candidates for antiobesity drug therapy.⁶⁵ Drug therapy is typically offered in conjunction with a program of physical activity, nutrition counseling, and behavior management. Liraglutide would represent a novel mechanism of action that provides an additional nonsurgical option to orlistat, phentermine-topiramate, lorcaserin, or naltrexone-bupropion for overweight and obese patients.

Figure 3. Overall high-impact potential: liraglutide (Saxenda) for treatment of obesity



Overall, experts commenting on this drug generally agreed that liraglutide has potential as a pharmacologic therapy for treating obesity. Most experts noted that other pharmacotherapies for treating obesity are available, but each has side effects and safety concerns. Liraglutide has the potential to improve patient health outcomes, some experts commented, citing fewer AEs than other available therapies. One research expert considered liraglutide to have a great potential to fulfill dual needs in treating diabetes and obesity. Some experts expressed concern about long-term safety, citing the history of discontinued antiobesity drugs (e.g., fenfluramine and phentermine [fen-phen]⁶⁶), but most experts anticipated widespread acceptance of this intervention by patients and clinicians alike, citing well documented off-label use of the drug. Some experts noted daily self-injection and gastrointestinal side effects to be potential deterrents to patients. Basing our evaluation on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on liraglutide.⁶⁷⁻⁷³ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: An important need exists for nonsurgical weight-loss options with favorable safety profiles, the experts generally agreed. This intervention has the potential to improve patient health outcomes by promoting weight loss and reducing obesity-related conditions such as diabetes mellitus, most experts commented. For instance, one expert representing a clinical perspective commented, “The weight loss seen with liraglutide at 3 mg daily appears to be at least 5% which should improve some obesity related comorbidities. The weight loss noted in the trials is similar to medications currently approved by the FDA.”⁶⁷ But several experts expressed concern regarding gastrointestinal side effects and listed a need for long-term studies to evaluate safety. And the durability of the drug’s effects was questioned by one expert representing a health systems perspective, who commented, “Short term improvements are promising however it is unclear if these improvements will persist long term.”⁷¹ Multiple experts commented that liraglutide is already widely used off label to treat obesity, which diminishes the unmet need. Although other pharmacotherapies are available for treating obesity, experts cited a significant unmet need for new treatments. One clinical expert opined, “Obesity causes numerous morbid conditions and increases mortality however, few durable, effective, pharmacologic options are available. Victoza (Saxenda) presents a potential pharmacologic option for treatment of this common disease.”⁷²

Acceptance and adoption: Liraglutide as a weight-loss option would be well accepted by both patients and clinicians, the experts generally agreed. One expert representing a research perspective commented, “Based on the off-label use numbers, there is a good chance that the drug will be widely adopted by physicians.”⁶⁸ Another research expert expressed optimism about the potential for a nonsurgical treatment for obesity, but cited the daily requirements of self-injection to be a deterrent to patient acceptance.⁶⁹ Other notable barriers to wide acceptance of liraglutide listed by experts were cost and the potential for gastrointestinal side effects. Several experts commented that patients would require initial training on how to properly self-inject the drug, but they did not anticipate this issue to be a barrier to acceptance.

Health care delivery infrastructure and patient management: Only a minor disruption to health care delivery infrastructure would be seen with liraglutide use, the experts generally agreed. Several experts listed patient education and training to have a potentially minor impact. For instance, an expert with a research perspective commented, “This medication is a self-administered

injection that is prescribed by either a PCP [primary care physician] or another clinician. Other than initial training on how to use the injection pen, there is no reason to anticipate disruption.”⁷⁴

Similarly, patient health management would not undergo a major disruption, the experts thought. One expert representing a health administration perspective commented that patients should be counseled regarding dietary and lifestyle changes when using this intervention.⁷¹

Health disparities: Health disparities could increase because the cost of this intervention and its lack of insurance coverage might serve as barriers to access for uninsured and low-income patient populations, the experts generally agreed. Along this line of reasoning, one expert representing a research perspective opined, “Since anti-obesity drugs are not typically covered by third-party payers (except for specific patient populations with comorbidities), patients will typically have to bear the costs of the drug. Thus patients with lower economic status may not have access to the drug.”⁶⁸

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