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Obesity Devices

Emerging Concepts and Novel Approaches

Impacted Companies

Allergan (AGN)
EnteroMedics (ETRM)
GI Dynamics (privately held)
Johnson & Johnson (JNJ)

About the Expert

Bruce Wolfe, M.D. is a professor of surgery at Oregon Health and Science University and the Co-chair of the National Institute of Health Research Consortium on Bariatric Surgery (also known as LABS). He is also the President-elect of the American Society of Metabolic and Bariatric Surgery.

- The surgical treatment of obesity has demonstrated significant ancillary benefit in diabetes, hypertension, sleep apnea, and other disorders.
- Discussing the state of the art of obesity devices, Dr. Bruce Wolfe highlighted GI Dynamics' duodenal sleeve and EnteroMedics' (ETRM) nerve blocking system.
- The medical community is increasingly open to treating patients with lower body mass index (BMI). A lowering of the BMI surgical standard to 30 from 35 would more than double the market potential of obesity devices.
- Minimally invasive options have expanded patient interest.
- Dr. Wolfe believes that EnteroMedics' next study evaluating its vagal nerve blocking device will produce positive results. He believes the previous study failed because of trial design issues.
- New pharmacologic therapies for obesity are unlikely to limit the market potential of devices.

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Speaking for the *in*Thought Expert Discussion Series, Dr. Bruce Wolfe outlined several novel approaches in the surgical treatment of obesity.

Introduction

Less than five years ago, Medicare changed its obesity guidelines, referring to obesity as a disease that is necessary to treat. Research in the last ten years has led to a better understanding of the health effects of severe obesity. This has, in turn, sparked significant improvements in treatment, mainly due to bariatric surgery.

One key paper, published in *The New England Journal of Medicine* last July (361:445-454) showed low mortality and morbidity associated with obesity procedures. Gastric banding had a zero mortality rate in the published study. Many studies have indicated the benefits of bariatric surgery, often demonstrating a dramatic reduction in the incidence of diabetes, cardiovascular disorders, etc. Technical advances such as laparoscopic surgery have increased the adoption of surgical intervention for obesity.

Given the demonstrated benefits of weight loss achieved by surgery, there is interest in extending technology to more people so that long-term health risks are reduced. That is feasible now because the technology has become simpler, cheaper, and safer. Initially, open gastric bypass was the surgical intervention of choice, but difficulties operating on the severely obese caused surgeons to look for other techniques. Once these techniques were worked out, they became widely popular. The current minimally invasive banding techniques by Allergan and Johnson & Johnson are preferred, with few differences between the two devices, according to Dr. Wolfe.

Improvement or remission of diabetes can be induced via gastric banding in people with BMI of 30 or lower.

In 1991, the National Institutes of Health (NIH) set qualifying criteria for bariatric surgical intervention as a body mass index (BMI) of 35 with severe co-morbidity such as diabetes, hypertension, or sleep apnea. Bariatric surgery was also indicated for anyone with a BMI of 40 or greater. Since then, the benefits of bariatric surgical intervention have become clear, suggesting that patients with lower BMIs could also benefit.

A study published in September of last year showed improvement or remission of diabetes can be induced via gastric banding in BMI 30 or even lower subjects (*Obes Surg*. 2009 Sep 9, "The Use of an Improved Intragastric Balloon Technique to Reduce Weight in Pre-obese Patients-Preliminary Results," Carvalho, et al.) Lowering the standard BMI to 30 from 35 would more than double the number of potential candidates for bariatric surgery. The problem comes in that managed care may not be willing to cover lower BMI patients until long-term data are available. Current obesity surgery clinical trials do not test less obese subjects. Patients' average BMI is in the upper 40s. Trial sponsors have less incentive to study lower BMI subjects since absolute weight loss is likely to be lower.

Novel Devices and Emerging Concepts

Dr. Wolfe highlighted several devices with the potential to change or expand the market. One device is a duodenal sleeve being developed by GI Dynamics. It is a two-foot long Teflon-like, flexible tube that lines the duodenum, causing the mucosa of the duodenum and proximal jejunum to avoid nutrient contact, thereby not being absorbed into the body. **Dr. Wolfe believes that the novel sleeve device is likely to not only impact the weight of the patient, but also benefit their diabetes.**

Last year, a study presented at the American Diabetes Association meeting showed that average daily glucose levels declined significantly after the sleeve was implanted. Dr. Wolfe does have some concerns, as the device may block the gastric outlet, essentially obstructing the stomach and causing people to eat less, but potentially leading to obstructive consequences such as vomiting and pain. Also, there is a question as to how long the sleeve can be left in the body and the frequency with which it can be safely changed. Although it will require some investigation, Dr. Wolfe believes the duodenal sleeve is innovative and worthy of further study.

Gastric stimulation, vagal stimulation, and vagal blocking were also identified as interesting potential therapies by Dr. Wolfe, with a particular focus on EnteroMedics' vagal nerve blocker. The initial trials of the EnteroMedics device, performed in Australia, showed weight loss with the device compared to baseline.

More recently, a larger trial used a sham-controlled comparator, meaning that all patients were

implanted with the device but half the patients did not have the device turned on. This trial did not meet its endpoint. Dr. Wolfe believes this is because the control group lost weight, citing it as the most invasive sham-controlled trial to date. He believes that the study was not long enough for the sham-effect to wear off, or that there is some effect on the vagus nerves from simply implanting the device. Either way, the next trial is likely to have more appropriate endpoints that can demonstrate the effectiveness of the device.

Although nerve stimulation to treat obesity is interesting, not enough is known about the biochemistry and neurology of the approach. If successful, vagal blocking will compete with vagotomy, which is relatively easy to do. There are some papers about vagotomy having transient success at inducing weight loss. The blocking device would have better efficacy since the nerve is not altered or removed, reducing the chance that the brain could compensate for the lack of signal. Dr. Wolfe notes that both blocking and stimulating the vagal nerve have been explored as obesity treatments, highlighting how poorly the physiology is understood.

Clinical Trial Design

According to Dr. Wolfe, one problem with obesity trial design is that a meaningful outcome metric should be required in addition to weight loss. This could be reduction in heart attack or stroke, for example. These hard endpoints require longer and larger trials, so cardiovascular risk markers are being developed for obesity trials. The most common cardiovascular risk scheme comes from the Framingham study, which didn't initially even track BMI. Cardiovascular risk assessment could provide important evidence of efficacy in obesity trials.

There is also a need to identify subgroups that are better suited to a gastric balloon vs. gastric banding vs. gastric stimulation vs. vagal blocking. In addition, methods should be developed to identify candidates for devices vs. drugs.

Pharmacological Therapy

The goal of pharmacotherapy for obesity aims at reducing weight, maintaining lost weight, and reducing the risk of associated co-morbidities.

To date, anti-obesity agents have not proven as effective as surgical intervention. Current drug treatment options are poorly tolerated and modestly efficacious, offering weight loss on the order of 3-5% over a one year period, and often associated with weight regain. Failure rates are high and cost is considerable. Moreover, these agents continue to be plagued by safety concerns.

Last month, the European Medicine Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the suspension of Abbott's Meridia (sibutramine). The panel indicated that a safety review found the compound to be associated with an increased risk of cardiovascular events, compared with placebo.

Vivus's Qnexa, Arena's lorcaserin and Orexigen's Contrave are approaching regulatory approval, but *in*Thought does not anticipate any of these will limit use of surgical devices.

Conclusion

A growing obese population across the globe, a developmental pipeline of novel, less invasive devices, and a medical community that has become accepting of surgical obesity interventions make the obesity device space uniquely positioned for growth. Few pure-play options make small companies like EnteroMedics particularly attractive.