Vagus Nerve Blocking Therapy for Treatment of Obesity

Policy Number: 7.01.150  Last Review: 4/2017  

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Vagal Nerve Blocking Therapy for Treatment of Obesity. This is considered investigational.

When Policy Topic is covered
n/a

When Policy Topic is not covered
Intra-abdominal vagal nerve blocking therapy is considered investigational in all situations, including but not limited to the treatment of obesity.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<td></td>
<td>• With obesity</td>
<td>• Conservative care ie diet, exercise</td>
<td>• Change in disease status</td>
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<td></td>
<td>• Vagal nerve blocking therapy</td>
<td>• Pharmacologic therapy</td>
<td>• Morbid events</td>
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<td>• Surgery</td>
<td>• Quality of life</td>
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Vagal nerve blocking therapy for obesity consists of an implantable device that delivers electrical stimulation to branches of the vagus nerve on the anterior abdominal wall. The intent is to cause intermittent blocking of signals to the intra-abdominal vagus nerve to disrupt hunger sensations and induce feelings of satiety.

For individuals who have obesity who receive vagus nerve blocking therapy, the evidence includes 2 sham-controlled randomized trials. Relevant outcomes are change in disease status, morbid events, quality of life, and treatment-related morbidity. The primary efficacy outcome (at least a 10% difference between groups at 12 months) was not met for either trial. In the first trial (EMPOWER), the observed difference in excess weight loss (EWL) between groups at 12 months
was 1%. In the more recent trial (ReCharge), the observed difference in EWL between groups at 12 months was 8.5%; a post hoc analysis found this difference statistically significant, but the magnitude of change may not be viewed as clinically significant according to investigators’ original trial design decisions. Post hoc analyses of longer term data have been published and are subject to various biases including missing data and unblinding at 12 months. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

Obesity is a common condition in the United States. A large nationally representative survey conducted in 2009 to 2010 found that 35% of American adults age 20 and older were obese, defined as body mass index (BMI) of 30 kg/m² or more.¹ Fifteen percent of adults had a BMI of 35 kg/m² or more and 6% had a BMI of 40 kg/m² or more. Among children age 2 to 19 years, 16.9% were obese, defined in the pediatric population as 95% percentile or more in BMI for age.

Obesity is a major cause of premature death and is linked to serious illnesses including heart disease, type 2 diabetes, sleep apnea, osteoarthritis, and certain types of cancer. In meta-analyses, being obese has been associated with higher all-cause mortality and death from cardiovascular disease.² In 2013, the American Medical Association officially recognized obesity itself as a disease.

Lifestyle interventions, specifically changes to diet and exercise, are the first-line treatment of obesity. These interventions can be enhanced by participation in a structured weight loss program and/or by psychological interventions such as cognitive behavioral therapy. There are also prescription weight loss medications, most notably orlistat (which blocks digestion and absorption of fat) and lorcaserin (which decreases appetite and promotes satiety). Weight loss medications have limited evidence of efficacy and there are associated adverse effects, eg, oily stool, nausea, and dizziness.

Weight loss (bariatric) surgery is a potential option for obese patients who have failed conservative treatments. Common procedures include gastric bypass surgery (open or laparoscopic approaches), sleeve gastrectomy, and laparoscopic adjustable gastric banding. Certain types of bariatric surgery have been found to improve outcomes in selected patients who choose that treatment.

Vagus nerve blocking therapy is another potential treatment option for obese patients. The vagus nerve consists of 2 long cranial nerves that extend from the brain stem to the viscera. The term *vagus* is Latin for wandering and the vagus nerve winds through the abdomen and has branches that come in contact with the heart, lung, stomach, and other body parts. The vagus nerve plays a major role in autonomic and sympathetic nervous systems including regulation of heartbeat and breathing. It is also involved in regulation of the digestive system, although its exact role in controlling appetite and feelings of satiety is unknown. Vagal nerve blocking therapy involves intermittent blocking of signals to the intra-abdominal
vagus nerve, with the intent disrupting hunger sensations and inducing feelings of satiety.

In January 2015, the U.S. Food and Drug Administration (FDA) approved a medical device specifically designed to provide vagal nerve blocking therapy for regulation of weight in obese patients. This device, the Maestro Rechargeable System, includes a neuroblocking pulse generator that is implanted subcutaneously on the thoracic sidewall and flexible leads approximately 47 cm in length that are placed on the abdominal anterior and posterior vagal nerve trunks. External components include a mobile charger, a transmit coil, a programmable microprocessor, and customized software. The system delivers high-frequency pulses of electrical current to vagus nerve trunks; therapy parameters and the treatment schedule can be customized by a clinician. Like other surgical interventions, there is the potential for adverse effects. In addition, there may be other unintended consequences of disrupting signals to a particular portion of the vagus nerve.

(Stimulation of the vagus nerve via a device implanted within the carotid artery sheath has also been evaluated as a treatment for obesity and is addressed in a separate policy. Vagus nerve stimulation is FDA-approved to treat epilepsy and depression, not for obesity treatment.)

**Rationale**

This evidence review was originally created in April 2015 and has been updated regularly with a search of the MEDLINE database. The most recent literature update covers the period through December 20, 2016.

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes compared with available alternatives.

In the case of interventions to treat obesity, a double-blind RCT is optimal because these interventions require changes to patient behavior (ie, diet, exercise) that are subject to the placebo effect. Health outcomes such as mortality, cardiovascular events, and rates of type 2 diabetes would be optimal, but are difficult to use as study end points due to the need for a large sample size and long follow-up period. Cardiovascular risk factors, such as changes in blood pressure, glucose, and lipid levels, are good intermediate measures because they have been linked with these health outcomes, and would require smaller sample sizes. Weight loss outcomes, reported as absolute change in weight or body mass index (BMI), or as percent excess weight loss (EWL) or percent BMI are acceptable intermediate outcome measures and are commonly used in obesity studies. Weight loss has been linked to improvements in cardiovascular risk factors. While no generally accepted threshold of percent EWL is considered clinically significant, bariatric surgery trials generally define clinical success as at least 50% EWL. The amount of weight loss is expected to be lower for other, less dramatic weight loss interventions.
Sham controls are useful for establishing the efficacy of an intervention beyond the placebo effect and for controlling for other nonspecific effects of interventions including disease natural history and regression to the mean. Because there are so many existing treatment options for weight loss, if sham-controlled weight loss intervention studies are positive, trials using an active comparator, such as medication or other types of surgery, are desirable.

**Vagus nerveBlocking therapy for obesity**
The published literature on vagus nerve blocking for obesity consists of 2 RCTs, both of which were industry-sponsored, multicenter, double-blind, and sham-controlled.\(^3\)\(^4\) Although both trials included a sham treatment group, protocols differed. In the 2012 EMPOWER trial, all participants had devices implanted and leads placed.\(^3\) However, external controllers were programmed differently such that if the controllers were worn for 10 hours a day, the total charge delivered was 3.9 coulombs (C) to patients in the treatment group and a negligible amount (0.0014 C), to the sham group. In the 2014 ReCharge trial, all participants had devices implanted, but no leads were placed in the sham group.\(^4\)

Study characteristics and results of the 2 trials are summarized in Tables 1 and 2, respectively.

**Table 1: RCTs Evaluating Vagus Nerve Blocking for Treatment of Morbid Obesity: Characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>EMPOWER (Sarr et al, 2012)(^3)</th>
<th>ReCharge (Ikramuddin et al, 2014)(^4)</th>
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<tbody>
<tr>
<td>No. patients randomized</td>
<td>294</td>
<td>239</td>
</tr>
<tr>
<td>Age range, y</td>
<td>18-65</td>
<td>18-65</td>
</tr>
</tbody>
</table>
| Key eligibility criteria  | • BMI 40-45 kg/m\(^2\) or 35-39.9 kg/m\(^2\) with ≥1 obesity-related comorbid conditions  
                             • Failed to respond to supervised diet/exercise program (timeframe not specified)  
                             | • BMI 40-45 kg/m\(^2\) or 35-40 kg/m\(^2\) with ≥1 obesity-related comorbid conditions  
                             • Failed to respond to supervised diet/exercise program within past 5 y |
| Intervention              | Maestro device plus 15 weight management counseling sessions (n=192) | Maestro device plus 17 weight management counseling sessions (n=162) |
| Comparator                | Sham with Maestro device plus 15 weight management counseling sessions (n=102) | Sham with Maestro device plus 17 weight management counseling sessions (n=77) |
| Outcome measures          |                                   |                                         |
| Primary                   | Difference in mean percent EWL at 12 mo (superiority margin: 10%)  
                             | ≥55% of patients in active treatment group achieved 20% EWL; ≥45% achieved 25% EWL  
                             |                                         |
| Secondary                 | Difference in percent of patients who achieved ≥25% EWL  
                             |                                         |
| Safety                    | Rate of SAEs  
                             | SAEs <15% in active treatment group |
Follow-up, mo 12 12

BMI: body mass index; EWL: excess weight loss (calculated as difference between pre- and posttreatment weights divided by difference between pretreatment weight and ideal body weight. BMI of 25 kg/m^2 was considered ideal); RCT: randomized controlled trial; SAE: serious adverse event.

Table 2: RCTs Evaluating Vagus Nerve Blocking for Treatment of Morbid Obesity: Results

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>EMPOWER (Sarr et al, 2012)^3</th>
<th>ReCharge (Ikramuddin et al, 2014)^4</th>
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<tbody>
<tr>
<td></td>
<td>Active Mean Percent EWL</td>
<td>Sham Mean Percent EWL</td>
</tr>
<tr>
<td></td>
<td>17%</td>
<td>16%</td>
</tr>
<tr>
<td>Difference</td>
<td>1% (p=NS)</td>
<td>24.4%</td>
</tr>
<tr>
<td></td>
<td>Active Mean Percent EWL</td>
<td>Sham Mean Percent EWL</td>
</tr>
<tr>
<td>Primary efficacy</td>
<td>24.4%</td>
<td>15.9%</td>
</tr>
<tr>
<td></td>
<td>8.5% (p=0.71^a)</td>
<td></td>
</tr>
<tr>
<td>≥25% EWL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary efficacy</td>
<td>22%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>No. of SAEs</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Percentage of SAEs</td>
<td>3.7%^b</td>
<td>NR</td>
</tr>
</tbody>
</table>

EWL: excess weight loss (calculated as difference between pre- and posttreatment weights divided by difference between pretreatment weight and ideal body weight. BMI of 25 kg/m^2 was considered ideal); NR: not reported; RCT: randomized controlled trial; SAE: serious adverse event.

^a For a >10% difference.

^b Met objective of <15%.

The primary efficacy outcomes were not met in either RCT. The difference in mean percent EWL was the sole primary efficacy outcome in the EMPOWER study and a coprimary outcome in the ReCharge study. This outcome was evaluated in both trials using a superiority margin of 10% (ie, the efficacy objective would be met only if there was >10% difference between groups in EWL). U.S. Food and Drug Administration (FDA) documents have indicated that the unattained 10% margin was considered to indicate a clinically meaningful difference in weight loss between active and sham treatment groups.⁵

For the ReCharge trial, however, in addition to the primary efficacy analysis, the authors also conducted a post hoc analysis that evaluated the difference in EWL between groups using a 2-sided t test with no superiority margin. In this post hoc analysis, the difference between groups (8.5% EWL; 95% CI, 3.1% to 13.9%) was statistically significant. (The difference between groups in percent EWL in the EMPOWER study was 1%.)

The outcome used in these studies was percent EWL, and modest changes in this outcome may translate to a relatively small amount of weight loss relative to total weight for patients with morbid obesity. Mean initial body weight in the ReCharge trial was 113 kilograms (249 pounds) in the active treatment group and 116 kilograms (255 pounds) in the sham group. Mean excess body weight was 44 kilograms (97 pounds) in the treatment group and 45 kilograms (99 pounds) in the sham group. Thus, a difference of 10% EWL, used in the primary analyses, represents a difference of only about 5 kilograms (10 pounds) in absolute weight loss and a 4% difference in absolute body weight.
The ReCharge study had a second primary outcome, which would have been met if at least 55% patients in the active treatment group had achieved at least 20\% EWL and at least 45\% had achieved at least 25\% EWL. This outcome was not achieved; the data showed that 52\% of patients in the active treatment group achieved at least 20\% EWL and 38\% achieved at least 25\% EWL. In the EMPOWER study, groups did not differ significantly on the secondary outcome measure (percent of patients achieving at least 25\% EWL).

In post hoc subgroup analysis of the EMPOWER trial, longer duration of device use per day was associated with a larger percent EWL. However, this improvement occurred in the sham group as well as the active treatment group. For example, percent EWL among patients who used the device for less than 6 hours a day was 5\% in the active treatment group and 6\% in the sham group, whereas percent EWL among patients who used the device for at least 12 hours a day was 30\% and 22\%, respectively. This finding suggests a substantial placebo effect associated with device use.

Both trials met their primary safety outcomes, which related to SAEs. However, there were frequent nonserious adverse events. Rates of key adverse events (all severity levels) in the ReCharge trial are shown in Table 3. Most were of mild or moderate severity. The authors of the EMPOWER trial did not report individual adverse events.

### Table 3: Most Common Adverse Events, ReCharge Trial

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>No. (%) of Patients</th>
<th>Treatment Group (n=162)</th>
<th>Sham Group (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain, neuroregulator site</td>
<td>61 (38%)</td>
<td>32 (42%)</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>38 (23%)</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>Pain, other</td>
<td>37 (23%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pain, abdominal</td>
<td>20 (12%)</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (7%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>13 (8%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Belching</td>
<td>13 (8%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Additional information on the ReCharge trial design and findings has been reported in FDA documents.\(^5\) The trial was designed to evaluate primary end points at 12 months and to follow patients to 5 years postimplant. Patients were blinded until 12 months and unblinding began once all patients had completed the 12-month follow-up. After the 12-month follow-up, sham patients had the option to cross over into the active treatment group. At 18 months, follow-up data (n=159) were reported for 117 (72\%) patients initially assigned to the active treatment group and 42 (55\%) assigned to the sham treatment group. The number of patients in the sham group who crossed over to active treatment and the timing of unblinding were not reported. At 18 months, the mean percent EWL was 25.3\% in the active treatment group and 11.7\% in the sham group; the mean between-group difference was 13.5\% (95\% confidence interval [CI], 5.7\% to 21.3\%). In this
analysis, the treatment group maintained the weight loss they achieved at 12 months, and the control group gained weight. Nearly half of the patients initially randomized to the sham group were not included in the 18-month analysis, which limits ability to draw conclusions about these data. In addition, the 18-month analysis could have been biased by unblinding, which occurred after all patients who completed the 12-month follow-up. In the 12-month sham intervention phase of the trial, patients in both groups experienced decreased hunger, increased cognitive restraint, and decreased food intake. It is likely that unblinding could have had an impact on these factors. FDA documents also reported longer term safety data. Analyses of data up to 48 months from the EMPOWER trial and 18-month data from the ReCharge trial did not identify any deaths or unanticipated serious adverse events. There were 13 surgical explants through 12 months (5 in active treatment group, 8 in sham group) and an additional 16 explantations between 12 and 18 months. Reasons for explant included patient decision, pain, and need for magnetic resonance imaging.

Eighteen-month follow-up data from the ReCharge trial were published by Shikora et al in 2015. They reported on a larger proportion of the patient population than that discussed in the FDA documents: in addition to the 159 (67%) of 239 randomized patients who completed the 18-month follow-up, the 2015 analysis included 30 patients who missed the 18-month analysis but had a visit at 16 or 17 months. The additional patients included 11 from the active treatment group and 19 from the sham group, comprising 188 patients (79% of those originally randomized). At 18 months, the mean percent EWL noted was 23.5% (95% CI, 20.8% to 26.3%) in the active treatment group and 10.2% (95% CI, 6.0% to 14.4%) in the sham group. The mean between-group difference in percent EWL was 13.4% (95% CI, 8.4% to 18.4%). The authors also evaluated the potential impact of blinding on outcomes and found no statistically significant effect; their findings were similar to the analysis restricted to patients who remained blinded at 18 months. The percentages of EWL at 18 months in this 2015 analysis of ReCharge trial data were also similar to those previously reported in FDA documents, although this sample size was larger, reducing potential bias from missing data. However, because this post hoc analysis incorporated 16- and 17-month data in addition to 18-month data, the authors considered these results preliminary or hypothesis-generating.

Twenty-four-month outcomes from ReCharge were published by Apovian et al in 2016. The investigators noted that the sham arm was no longer a valid comparator at 24 months due to crossovers, dropouts, and patient unblinded at 12 months. There was no prespecified statistical analysis plan for assessments after the 12-month primary outcome assessment, including those in this 2016 article. A total of 103 (43%) patients of 239 randomized patients completed the 24-month follow-up. Their mean EWL was 21% (95% CI, 16% to 26%) and mean total weight loss was 8% (95% CI, 6% to 10%). No serious treatment-related adverse events were reported in the 18- to 24-month time period. The analysis lacked a blinded comparison group, and, like the 18-month data, was post hoc.
Section Summary: Vagus Nerve Blocking Therapy for Obesity
Two sham-controlled RCTs have been published. The primary efficacy outcome (at least a 10% difference between groups) was not met for either trial. In the first trial (EMPOWER), the observed difference in EWL between groups at 12 months was 1%. In the more recent trial (ReCharge), the observed difference in EWL between groups at 12 months was 8.5%; a post hoc analysis found this difference statistically significant, but the magnitude of change may not be viewed as clinically significant according to investigators’ original trial design decisions. Additional analyses of data from ReCharge found a difference in EWL at 18 months of approximately 13% in 79% of initially randomized patients and a mean EWL of 21% at 24 months in 43% of initially randomized patients. However, analyses beyond 12 months were post hoc, considered preliminary, and need to be replicated in other appropriately designed RCTs. In addition, the 18- and 24-month data have potential biases, including missing data and unblinding. Moreover, the 18-month analysis combined data from different follow-up visits and the 24-month analysis lacked a control group. The 2 RCTs found that vagus nerve blocking was reasonably safe in terms of serious adverse events during follow-up, although a substantial number of mild and moderate adverse events were reported.

Summary of Evidence
For individuals who have obesity who receive vagus nerve blocking therapy, the evidence includes 2 sham-controlled randomized trials. Relevant outcomes are change in disease status, morbid events, quality of life, and treatment-related morbidity. The primary efficacy outcome (at least a 10% difference between groups at 12 months) was not met for either trial. In the first trial (EMPOWER), the observed difference in excess weight loss (EWL) between groups at 12 months was 1%. In the more recent trial (ReCharge), the observed difference in EWL between groups at 12 months was 8.5%; a post hoc analysis found this difference statistically significant, but the magnitude of change may not be viewed as clinically significant according to investigators’ original trial design decisions. Post hoc analyses of longer term data have been published and are subject to various biases including missing data and unblinding at 12 months. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements
A position statement published in 2016 by the American Society for Metabolic and Bariatric Surgery includes the following conclusions and recommendations on vagus nerve blocking therapy for treatment of obesity:

“1. Reversible vagal nerve blockade has been shown to result in statistically significant EWL [excess weight loss] at 1 year compared with a control group in one of 2 prospective randomized trials.

2. Reversible vagal nerve blockage has been shown to have a reasonable safety profile with a low incidence of severe adverse events and a low
revisional rate in the short term. More studies are needed to determine long-term reoperation and explantation rates.

3. The prospective collection of VBLOC [vagus nerve blocking] outcomes as part of the national center of excellence databases is encouraged to establish the long-term efficacy of this new technology.”

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force (USPSTF) published recommendations for screening and management of obesity in adults in 2012. USPSTF recommended screening all adults for obesity and referring those with a body mass index of 30 kg/m² or higher to intensive, multicomponent behavioral interventions. Vagus nerve blocking therapy and other surgical interventions were not addressed in the recommendations or literature review. As of December 30, 2016, the recommendations were being updated; no release date for the updated recommendations was provided.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in December 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

References
Billing Coding/Physician Documentation Information

0312T  Vagus nerve blocking therapy (morbid obesity); laparoscopic implantation of neurostimulator electrode array, anterior and posterior vagal trunks adjacent to esophagogastric junction (EGJ), with implantation of pulse generator, includes programming

0313T  Vagus nerve blocking therapy (morbid obesity); laparoscopic revision or replacement of vagal trunk neurostimulator electrode array, including connection to existing pulse generator

0314T  Vagus nerve blocking therapy (morbid obesity); laparoscopic removal of vagal trunk neurostimulator electrode array and pulse generator

0315T  Vagus nerve blocking therapy (morbid obesity); removal of pulse generator

0316T  Vagus nerve blocking therapy (morbid obesity); replacement of pulse generator

0317T  Vagus nerve blocking therapy (morbid obesity); neurostimulator pulse generator electronic analysis, includes reprogramming when performed

ICD-10 Codes:

E66.01  Morbid (severe) obesity due to excess calories

Additional Policy Key Words

N/A

Policy Implementation/Update Information

4/1/16  New policy; considered investigational.

4/1/17  Title changed from “Vagal” to “Vagus”. No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.