MEDICAL POLICY – 2.02.33
Phrenic Nerve Stimulation for Central Sleep Apnea

BCBSA Ref. Policy: 2.02.33
Effective Date: Nov. 1, 2019
Last Revised: July 9, 2019
Replaces: N/A

RELATED MEDICAL POLICIES:
None

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Central sleep apnea is a sleep disorder in which the brain briefly stops sending signals to the muscles that govern breathing. The typical way of treating central sleep apnea is to use a positive airway pressure device to blow pressurized air into the airway during sleep. A new technique of trying to treat sleep apnea is being studied. This technique calls for a specific nerve in the chest, the phrenic nerve, to be stimulated. A device is implanted and low levels of electricity are sent to the phrenic nerve. This is then supposed to stimulate the diaphragm. (The diaphragm is a large muscle beneath the lungs that expands and contracts as you breathe.) It’s thought that stimulating the diaphragm improves breathing during sleep. Phrenic nerve stimulation for central sleep apnea is investigational (unproven). More research is needed to see if this technique is safe, reliable, and effective.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
# Service

<table>
<thead>
<tr>
<th>Phrenic nerve stimulation</th>
</tr>
</thead>
</table>

## Investigational

The use of phrenic nerve stimulation for central sleep apnea is considered investigational in all situations.

## Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></td>
<td></td>
</tr>
<tr>
<td>0424T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; complete system (transvenous placement of right or left stimulation lead, sensing lead, implantable pulse generator)</td>
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<tr>
<td>0425T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
</tr>
<tr>
<td>0426T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; stimulation lead only</td>
</tr>
<tr>
<td>0427T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; pulse generator only</td>
</tr>
<tr>
<td>0428T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only</td>
</tr>
<tr>
<td>0429T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
</tr>
<tr>
<td>0430T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea; stimulation lead only</td>
</tr>
<tr>
<td>0431T</td>
<td>Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only</td>
</tr>
<tr>
<td>0432T</td>
<td>Repositioning of neurostimulator system for treatment of central sleep apnea; stimulation lead only</td>
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<tr>
<td>0433T</td>
<td>Repositioning of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
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<td>0434T</td>
<td>Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea</td>
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<tr>
<td>0435T</td>
<td>Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session</td>
</tr>
<tr>
<td>0436T</td>
<td>Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; during sleep study</td>
</tr>
</tbody>
</table>
Central sleep apnea (CSA) is characterized by sleep-disordered breathing due to diminished or absent respiratory effort. CSA may be idiopathic or secondary (associated with Cheyne-Stokes breathing, a medical condition, drugs, or high altitude breathing). The use of positive airway pressure devices is currently the most common form of therapy for CSA. An implantable device that stimulates the phrenic nerve in the chest is a potential alternative treatment. The battery-powered device sends signals to the diaphragm in order to stimulate breathing and normalize sleep-related breathing patterns.

Background

Central Sleep Apnea

CSA is characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. CSA may be idiopathic or secondary (associated with Cheyne-Stokes breathing, a medical condition, drugs, or high altitude breathing. Cheyne-Stokes breathing is common among patients with heart failure (HF) or who have had strokes and accounts for about half of the population with CSA. CSA is less common than obstructive sleep apnea. Based on analyses of a large community-based cohort in the Sleep Heart Health Study, the estimated prevalence of CSA and obstructive sleep apnea are 0.9% and 47.6%, respectively.¹ Risk factors for CSA include age (>65 years), male gender, history of heart failure (HF), history of stroke, other medical conditions (acromegaly, renal failure, atrial fibrillation, low cervical tetraplegia, and primary mitochondrial diseases), and opioid use. Individuals with CSA have difficulty maintaining sleep
and therefore experience excessive daytime sleepiness, poor concentration, morning headaches, and are at higher risk for accidents and injuries.

**Treatment**

The goal of treatment is to normalize sleep-related breathing patterns. Because most cases of CSA are secondary to an underlying condition, central nervous system pathology, or medication side effects, treatment of the underlying condition or removal of the medication, may improve CSA.

Treatment recommendations differ depending on the classification of CSA as either hyperventilation-related (most common, including primary CSA and those relating to HF or high altitude breathing) or hypoventilation-related (less common, relating to central nervous system diseases or use of nervous system suppressing drugs such as opioids).

For patients with hyperventilation-related CSA, continuous positive airway pressure (CPAP) is considered first-line therapy. Due to CPAP discomfort, patient compliance may become an issue. Supplemental oxygen during sleep may be considered for patients experiencing hypoxia during sleep or who cannot tolerate CPAP. Patients with CSA due to HF and with an ejection fraction >45% and who are not responding with CPAP and oxygen therapy, may consider bilevel positive airway pressure or adaptive servo-ventilation (ASV) as second-line therapy. Bilevel positive airway pressure devices have two pressure settings, one for inhalation and one for exhalation. ASV uses both inspiratory and expiratory pressure, and titrates the pressure to maintain adequate air movement. However, a clinical trial reported increased cardiovascular mortality with ASV in patients with CSA due to HF and with an ejection fraction <45%, and therefore, ASV is not recommended for this group,

For patients with hypoventilation-related CSA, first-line therapy is bilevel positive airway pressure.

Pharmacologic therapy with a respiratory stimulant may be recommended to patients with hyperventilation or hypoventilation CSA who do not benefit from positive airway pressure devices, though close monitoring is necessary due to the potential for adverse effects such as rapid heart rate, high blood pressure, and panic attacks.
Table 1: Description of Positive Airway Pressure Devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
<td>Considered first line therapy for patients with hyperventilation-related CSA.</td>
</tr>
<tr>
<td>BPAP</td>
<td>bilevel positive airway pressure (2 pressure settings - 1 for inhalation and 1 for exhalation)</td>
<td>Considered first line therapy for patients with hypoventilation-related CSA</td>
</tr>
<tr>
<td>ASV</td>
<td>adaptive servo-ventilation (titrates the inspiratory and expiratory pressure)</td>
<td>Not recommended for patients with CSA with heart failure and left ventricular ejection fraction ≤45%</td>
</tr>
</tbody>
</table>

Phrenic Nerve Stimulation

Currently, there is one phrenic nerve stimulation device approved by the Food and Drug Administration, the remede System (Respicardia, Inc.). The remede System is an implantable device that stimulates the phrenic nerve in the chest which sends signals to the diaphragm to restore a normal breathing pattern. A cardiologist implants the battery-powered device under the skin in the right or left pectoral region. The procedure is conducted using local anesthesia. The device has two leads, one to stimulate a phrenic nerve (either the left pericardiophrenic or right brachiocephalic vein) and one to sense breathing. The device runs on an algorithm that activates automatically at night when the patient is in a sleeping position and suspends therapy when the patient sits up. Patient-specific changes in programming can be conducted externally by a programmer.

Summary of Evidence

For individuals with CSA who receive phrenic nerve stimulation, the evidence includes one randomized controlled trial (RCT) and observational studies. The relevant outcomes are change in disease status, functional outcomes, and quality of life (QOL). The RCT compared the use of phrenic nerve stimulation to no treatment among patients with CSA of various etiologies. All patients received implantation of the phrenic nerve stimulation system, with activation of the system after 1 month in the intervention group and activation after 6 months in the control group. Activation is delayed one month after implantation to allow for lead healing. At 6 months follow-up, the patients with the activated device experienced significant improvements in several sleep metrics and QOL measures. At 12 months follow-up, patients in the activated device arm showed sustained significant improvements from baseline in sleep metrics and QOL. A subgroup analysis of patients with HF combined 6-month and 12-month data from patients in the intervention group and 12-month and 18-month data from the control group. Results from
this subgroup analyses showed significant improvements in sleep metrics and QOL at 12 months compared with baseline. Results from observational studies supported the results of the RCT. No RCTs were identified in which phrenic nerve stimulation was compared with the current standard of care, positive airway pressure or respiratory stimulant medication. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

A currently ongoing trial that might influence this review is listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT03238937</td>
<td>Treatment of Central Sleep Apnea in Patients with Heart Failure with a Cervically Implanted Phrenic Nerve Stimulator</td>
<td>40</td>
<td>Jul 2022</td>
</tr>
</tbody>
</table>

NCT: national clinical trial

Practice Guidelines and Position Statements

American Academy of Sleep Medicine

The American Academy of Sleep Medicine (2012) published a guideline on the treatment of central sleep apnea (CSA), based on results of a literature review and meta-analysis.\textsuperscript{10} Moderate evidence supported the use of continuous positive airway pressure or adaptive servo-ventilation to treat CSA related to congestive heart failure. Limited evidence was available for the use of positive airway pressure therapy (continuous positive airway pressure, bilevel positive airway pressure, adaptive servo-ventilation) to treat primary CSA; however, there is potential for ameliorating central respiratory events, risks are low, and the therapies are readily available. The use of phrenic nerve stimulation devices was not discussed in the guideline. An update to the guideline, published in 2016,\textsuperscript{11} adjusted the previous guideline, to warn that adaptive servo-ventilation is not recommended for individuals with CSA related to congestive heart failure with
ejection fraction <45%. The use of phrenic nerve stimulation as a treatment option was not addressed in the guideline.

**Medicare National Coverage**

There is no national coverage determination.

**Regulatory Status**

In October 2017, the Food and Drug Administration granted approval for the remede System (Respicardia, Inc; Minnetonka, MN) through the premarket approval application process. The approved indication is for treatment of moderate to severe CSA in adults. Product code: PSR.

**References**


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/01/19</td>
<td>New policy, approved July 9, 2019, effective November 1, 2019. New policy created with literature review through April 2019. The use of phrenic nerve stimulation for central sleep apnea is considered investigational in all situations.</td>
</tr>
</tbody>
</table>

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