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Phrenic Nerve Stimulation for Central Sleep Apnea

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Coverage

The use of phrenic nerve stimulation for central sleep apnea **is considered experimental, investigational and/or unproven** in all situations.

Policy Guidelines

None.

Description

Central sleep apnea (CSA) is characterized by sleep-disordered breathing due to diminished or absent respiratory effort. Central sleep apnea may be idiopathic or secondary (associated with 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.

Central Sleep Apnea

Central sleep apnea is characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. Central sleep apnea may be idiopathic or secondary (associated with a medical condition such as congestive heart failure, drugs, or high altitude breathing). Apneas associated with Cheyne-Stokes respiration are common among patients with heart failure (HF) or who have had strokes, and account for about half of the population with CSA. Central sleep apnea is less common than obstructive sleep apnea. Based on analyses of a large community-based cohort of participants 40 years of age and older 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 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, and 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 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 2 pressure settings, 1 for inhalation and 1 for exhalation. Adaptive servo-ventilation 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%, (2) 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 hyper- 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.

Phrenic Nerve Stimulation
Several phrenic nerve stimulation systems are available for patients who are ventilator dependent. These systems stimulate the phrenic nerve in the chest, which sends signals to the diaphragm to restore a normal breathing pattern. Currently, there is 1 phrenic nerve stimulation device approved by the U.S. Food and Drug Administration (FDA) for CSA, the remedē System (Zoll Medical). A cardiologist implants the battery-powered device under the skin in the right or left pectoral region using local anesthesia. The device has 2 leads; 1 to stimulate a phrenic nerve (either the left pericardiophrenic or right brachiocephalic vein) and 1 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.

Regulatory Status
In October 2017, the remedē System (Respicardia, Inc [now Zoll Medical]; Minnetonka, MN) was approved by the FDA through the premarket approval application process (PMA #P160039). The approved indication is for the treatment of moderate to severe CSA in adults. Follow-up will continue for 5 years in the post-approval study. FDA product code: PSR.

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Phrenic Nerve Stimulation for Central Sleep Apnea

Clinical Context and Therapy Purpose

The purpose of phrenic nerve stimulation (PNS) in individuals who have central sleep apnea (CSA) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with CSA. Central sleep apnea is characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. Individuals with CSA have difficulty maintaining sleep and therefore experience excessive daytime sleepiness, poor concentration, and morning headaches, and are at higher risk for accidents and injuries.

Interventions

The therapy being considered is PNS. This system stimulates the phrenic nerve in the chest, which sends signals to the diaphragm to restore a normal breathing pattern. The device activates automatically when the individual is in a sleeping position and suspends therapy when the individual sits up.

Comparators

The current first-line therapy is positive airway pressure. There are several devices providing positive airway pressure (Table 1).

Table 1. Description of Positive Airway Pressure Devices

Device	Description	Comments
CPAP	Continuous positive airway pressure	Considered first line therapy for patients with hyperventilation-related CSA
BPAP	Bilevel positive airway pressure (2 pressure settings - 1 for inhalation and 1 for exhalation)	Considered first line therapy for patients with hypoventilation-related CSA
ASV	Adaptive servo-ventilation (titrates the inspiratory and expiratory pressure)	Not recommended for patients with CSA with HC X and left ventricular ejection fraction <45%

CSA: central sleep apnea; HF: heart failure.

For individuals who do not benefit from positive airway pressure devices, pharmacologic therapy with a respiratory stimulant may be recommended. Close monitoring is necessary due to the potential of adverse effects such as rapid heart rate, high blood pressure, and panic attacks.

Outcomes

Outcomes of interest include sleep quality metrics and quality of life measures. The Apnea-Hypopnea Index (AHI) is the number of apnea and hypopnea (events per hour of sleep, in which the apnea events last at least 10 seconds and are associated with decreased blood oxygenation. In adults, the AHI scale is: <5 AHI (normal); 5≥AHI<15 (mild); 15≥ AHI<30 (moderate); and ≥30 AHI (severe) per hour of sleep. Additional sleep metrics include the central apnea index (CAI, number of central apnea events per hour of sleep) and obstructive apnea index (OAI, number of obstructive apnea events per hour of sleep).

Subjective sleepiness can be measured by the Epworth Sleepiness Scale (ESS). The ESS is a short, self-administered questionnaire that asks individuals how likely they are to fall asleep (0="no chance" to 3="high chance") in 8 different situations (e.g., watching TV, sitting quietly in a car, or sitting and talking to someone). The scores are added, ranging from 0 to 24, with scores over 10 indicating excessive sleepiness and recommendation to seek medical attention. Quality of life can be measured by Patient Global Assessment, which consists of a 7-point scale (1="markedly improved" to 7="markedly worsened").

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Wang et al. (2024) conducted a meta-analysis to evaluate the efficacy of PNS in individuals with CSA. (3) They conducted a systematic review up to December of 2021 and included 10 publications of RCTs and observational studies. Nine studies (n=351) reported AHI before and after PNS with a standard mean difference of -2.24 (95% CI: -3.11 to -1.36; p<.00001). Seven studies (n=332) reported CAI with a standard mean difference of -2.32 (95% CI: -3.17 to -1.47; p<.00001). Six studies (n=281) reported arousal index with a standard mean difference of -1.79 (95% CI: -2.74 to -0.85; p<.00001). Four studies (n=173) reported T90 with a standard mean difference of -0.54 (95% CI: -1.26 to 0.19; p<.00001). Three studies (n=104) reported sleep efficiency with a standard mean difference of 0.22 (95% CI: -0.26 to 0.69; p=.07). And 4 studies (n=186) reported ESS with a standard mean difference of -0.73 (95% CI: -1.59 to 0.14; p<.00001). A limitation of the meta-analysis is 4 of the publications used the same study cohort and another 2 publications used the same study cohort. The authors conclude the results of the meta-analysis indicates PNS may improve CSA, however, larger randomized studies are needed to assess long-term effects of PNS. Details on the systematic review are in Tables 2 to 4.

Table 2. Comparison of Studies Included in Systematic Reviews & Meta-Analyses

Study	Wang et al. (2024) (3)
Costanzo et al. (2021) (4)	●
Oldenburg et al. (2020) (5)	●
Costanzo et al. (2018) (6)	●
Zhang et al. (2017) (7)	● [a]
Fox et al. (2017) (8)	●
Jagielski et al. (2016) (9)	●
Costanzo et al. (2016) (10)	●
Abraham et al. (2015) (11)	●
Ponikowski et al. (2012) (12)	●
Zhang et al. (2012) (13)	●

[a] This study was identified in the systematic review but was not included in the overall meta-analyses.

Table 3. Systematic Reviews & Meta-Analyses Characteristics

Study	Dates	Trials	Participants[1]	N (Range)	Design	Duration
Wang et al. (2024) (3)	Up to December 2021	10	Individuals with CSA	580 (3 to 151)	RCTs and observational	1 night to 5 years

RCT: randomized controlled trial.

Table 4. Systematic Reviews & Meta-Analyses Results

Study	AHI	CAI	Arousal Index	T90	Sleep efficiency	ESS
Wang et al. (2024) (3)						
Total N	351	332	281	173	104	186
Pooled effect (95% CI)	SMD, -2.24 (-3.11 to -1.36)	SMD, -2.32 (-3.17 to -1.47)	SMD, -1.79 (-2.74 to -0.85)	SMD, -0.54 (-1.26 to 0.19)	SMD, 0.22 (-0.26 to 0.69)	SMD, -0.73 (-1.59 to 0.14)
I^2	96%	95%	96%	90%	63%	93%

AHI: Apnea-Hypopnea Index; CAI: central apnea index; CI: confidence interval; ESS: Epworth Sleepiness Scale; SMD: standardized mean difference; T90: percent of sleep with O2 saturation <90%.

Randomized Controlled Trial

Costanzo et al. (2015) provided background and methodologic details of the remedē System Pivotal Trial. (14) The trial is a prospective, multicenter, randomized, open-label controlled trial comparing transvenous unilateral phrenic nerve stimulation with no stimulation in patients with CSA of various etiologies (Table 5). All patients received implantation of the phrenic nerve stimulation system, with activation of the system after 1 month in the intervention group (n=73) and activation after 6 months in the control group (n=78). Activation is delayed 1 month after implantation to allow for lead healing. The primary efficacy endpoint was the percentage of patients achieving a reduction in AHI of 50%, as interpreted from polysomnography by an assessor blinded to the treatment arm. The reduction of 50% was based on assessments showing that a 50% reduction in AHI is associated with reduced mortality risk and is therefore

clinically meaningful. Secondary endpoints include mean reductions in CAI, AHI, arousal index, oxygen desaturation index, and ESS. Of the 151 patients in the trial, 64% had heart failure (HF), 42% had atrial fibrillation, with a mean left ventricular ejection fraction of 39.6%.

Costanzo et al. (2016) reported the 6-month per-protocol comparative results for the treatment and control groups (Table 6). (10) Twelve, 24-, and 36-month results for the intervention group are shown in Table 7. Adverse events were reported in 9% of the intervention group and 8% of the control group (for example, implant site infection, implant site hematoma, and lead dislodgement). Non-serious therapy-related discomfort was reported in 27 (37%) of the intervention group, with all but 1 case resolved by system reprogramming. At 6 months follow-up, 15 of the 73 (21%) patients in the treatment group were excluded due to no 6-month data: unrelated death, device explant, missed visit, and study exit (n=9), failed inclusion criteria (n=3), unsuccessful implant (n=2), and therapy programmed off (n=1).

At the 12-month follow-up, an additional 4 patients were lost due to unrelated death, device explant, patient refusal, and missed visits. Results from the remaining 54 patients in the intervention group at 12 months are summarized in Table 7. (15) Subgroup analyses showed consistent improvements in the percent experiencing more than 50% AHI reductions from treatment across all of the following subgroups: age (<65, 65 to <75, and >75), gender, HF (yes/no), defibrillator (yes/no), AHI severity (moderate/severe), and atrial fibrillation (yes/no). Follow-up at 24 months was available for 42 patients in the treatment group, while 22 patients in the treatment group and 28 patients in the control arm reached 36-month follow-up at the time of study closure. (16) Central apnea events remained low throughout follow-up with a median time to battery depletion of 39.4 months. Serious adverse events related to the implant procedure, device, or delivered therapy occurred in 10% of patients through the 24-month visit. All were reported to be resolved with remedē System revisions or programming. At the 5-year follow-up (N=52), AHI events remained low (median=17 events/hour), and ESS improved by a median of 3 points. (4) A total of 14% of patients reported a serious adverse event, but no long-term harm or device-related death occurred.

Several post hoc analyses have been reported from the remedē System Pivotal Trial further investigating the effects of transvenous phrenic nerve stimulation. Baumert et al. (2023) investigated treatment effect on the change in episodic hypoxemic burden between baseline and 6 months. (17) They found the treatment group (n=72) compared to the control group (n=62) had reduced oxygen desaturation index (ODI) (-15.85 ± 1.99 1/h vs. 1.32 ± 1.85 1/h; p<.0001) and shortened T90 (-3.81 ± 1.23 vs. 0.49 ± 1.14; p=.0121). In another paper by Baumert et al. (2023) they investigated the effect of treatment on nocturnal heart rate perturbations between baseline and 6 months. (18) They found the treatment group (n=22) compared to the control group (n=26) had reduced cyclical heart rate variations in the very low-frequency power index across rapid eye movement (REM) (4.12 ± 0.79% vs. 6.87 ± 0.82%; p=.02) and non-rapid eye movement (NREM) sleep (5.05 ± 0.68% vs. 6.74 ± 0.70%; p=.08). They also found normalized low-frequency power was reduced in the treatment arm in REM (0.67 ± 0.03 n.u. vs. 0.77 ± 0.03 n.u.; p=.02) and NREM sleep (0.70 ± 0.02 n.u. vs. 0.76 ± 0.02 n.u.; p=.03). Hartmann et al. (2023) studied the effects of treatment on sleep microstructure.

(19) They analyzed polysomnography data from baseline and 6 months. The treatment group (n=57) compared to controls (n=64) showed a decrease in the frequency of A2+A3 phases (-5.86 ± 11.82 vs. 0.67 ± 15.25; p=.006) and an increase in frequency of A1 phases (2.57 ± 11.67 vs. -2.47 ± 10.60; p=.011). Change in cyclic alternating pattern (CAP) rate at follow-up was comparable between both groups. The authors concluded transvenous phrenic nerve stimulation may affect sleep microstructure, however, further studies are need to better the understand these mechanisms. Samii et al. (2023) investigated sex differences in treatment effect over 12 months. (20) They found females (n=16) and males (n=135) experienced comparable improvements in CSA metrics, including improved sleep quality and architecture. At 12 months compared to baseline, females had improved AHI (median [Q1, Q3]: -21 [-24, -10] events/hour; p=.002), CAI (median [Q1, Q3]: -14 [-21, -10] events/hour; p=.002), and ESS scores (median [Q1, Q3]: -2 [-9, -1] points; p=.008), and males had improved AHI (median [Q1, Q3]: -22 [-40, -6] events/hour; p<.001), CAI (median [Q1, Q3]: -21 [-35, -12] events/hour; p<.001), and ESS scores (median [Q1, Q3]: -3 [-7, 0] points; p<0.001). However, this study was limited by the small number of females and the study was not powered to detect sex-specific differences in outcomes.

Table 5. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Intervention	**Control**
Costanzo et al. (2015) (14)	Germany, Poland, United States	31	2013-2015	Adult patients with moderate to severe CSA of various etiologies confirmed by PSG[a] and medically stable[b]	Implanted phrenic nerve stimulator (remedē system) activated at 1-month postprocedure (n=73, 58 analyzed)	Implanted phrenic nerve stimulator (remedē system) activated at 6 months postprocedure (n=78, 73 analyzed)
Baumert et al. (2023) (17)	NR	31	NR	Adult patients with moderate to severe CSA of various etiologies confirmed by PSG[a] and who had PSG data at the visit of interest	Implanted phrenic nerve stimulator (remedē system) on (n=72)	Implanted phrenic nerve stimulator (remedē system) off (n=62)

AHI: apnea-hypopnea index; CAI: central apnea index; CSA: central sleep apnea; NR: not reported; OAI: obstructive apnea index; PSG: polysomnography; RCT: randomized controlled trial.

[a] AHI >20 events/hr; CAI >50% of all apneas, with >30 central apnea events; OAI <20% of all AHI.

[b] For 30 days prior to baseline testing: no hospitalizations for illness, no breathing mask-based therapy, and on stable medications and therapies.

Table 6. Summary of Key RCT Results[a]

Study	Baseline	6-Month	Change from Baseline	Between Group Difference
Costanzo et al. (2015, 2016) (14, 10)				
>50% AHI reduction				
Treatment	NA	51% (39% to 64%)	NA	
Control	NA	11% (5% to 20%)	NA	41% (25% to 54%)
AHI				
Treatment	49.7 ± 18.9	25.9 ± 20.5	-23.9 ± 18.6	
Control	43.9 ± 17.3	45.0 ± 20.3	1.1 ± 17.6	-25.0 ± 18.1
CAI				
Treatment	31.7 ± 18.6	6.0 ± 9.2	-25.7 ± 18.0	
Control	26.2 ± 16.2	23.3 ± 17.4	-2.9 ± 17.7	-22.8 ± 17.8
PGA[b]				
Treatment	NA	60% (47% to 73%)	NA	
Control	NA	6% (2% to 14%)	NA	55% (40% to 68%)
ESS				
Treatment	10.7 ± 5.3	7.1 ± 4.1	-3.6 ± 5.6	
Control	9.3 ± 5.7	9.4 ± 6.1	0.1 ± 4.5	-3.7 ± 5.0
Baumert et al. (2023) (17)				
ODI				
Treatment	NA	23.70 ± 1.99	-15.85 ± 1.99	NA
Control	NA	40.87 ± 1.85	1.32 ± 1.85	NA
T90				
Treatment	NA	7.96 ± 1.23	-3.81 ± 1.23	NA
Control	NA	12.26 ± 1.14	0.49 ± 1.14	NA

AHI: Apnea-Hypopnea Index; CAI: central apnea index; CI: confidence interval; ESS: Epworth Sleepiness Scale; NA: not applicable; NR: not reported; ODI: oxygen desaturation index; PGA: Patient Global Assessment; RCT: randomized controlled trial; T90: percent of sleep with O2 saturation <90%.

[a] Data are presented as either % (95% CIs) or mean (standard deviation).

[b] Patients with marked or moderate improvement in 7-point quality of life scale.

Costanzo et al. (2018) provided 12-month follow-up results for the subgroup of patients in the Pivotal Trial who had HF. (21) Pooling of results was possible by using 6 and 12-month data from the intervention group and 12 and 18-month data from the control group (the phrenic nerve stimulator was activated in the control group 6 months after implantation). At baseline, 96 of the patients in the trial had HF. By the 6-month follow-up, there had been 4 deaths, 1 explant, and 5 withdrew from the study. By the 12-month follow-up, there had been an additional 5 deaths, 1 ex plant, and 1 withdrawal, as well as 4 missing the final visit. Results at 6- and 12-months follow-up for the subgroup of patients with HF are summarized in Table 7.

Hill et al. (2023) also conducted a subgroup analysis in individuals with CSA and HF (n=75) from the Pivotal Trial, investigating the effect of treatment on sleep, quality of life, and symptoms between baseline and 12 months using self-reported questionnaires. (22) Improvements were seen in 69% of individuals in ESS scores, 60% of individuals in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores, and 53% of individuals in Fatigue Severity Score (FSS) scores.

Table 7. Summary of Treatment Arm Results at Follow-up

	Baseline	**6-Month**	**12-Month**	**24-Month Median [IQR]**	**36-Month Median [IQR]**	**Paired Change, Baseline to 12-Month Mean (95% CI)**
Costanzo et al. (2018) (14, 15)						
Treatment arm alone, N	58	58	54	42	22[a]	54
AHI	49.7 ± 18.9	25.9 ± 20.5	23.0 ± 21.9	16 [7, 37]	13 [8, 37]	-25.4 (-44.4 to -11.4)
CAI	31.7 ± 18.6	6.0 ± 9.2	3.4 ± 6.9	0 [0, 3]	1 [0, 3]	-26.0 (-40.2 to -14.6)
OAI	2.1 ± 2.2	6.3 ± 7.0	4.5 ± 5.1	3 [0, 8]	4 [1, 11]	0.9 (-0.5 to 4.4)
PGA[b]	NA	60% (47% to 72%)	60% (47% to 72%)			NA
ESS	10.7 ± 5.3	7.1 ± 4.1	6.5 ± 3.5			-4.0 (-7.0 to -1.0)
Costanzo et al. (2018) (21)						
Pooled HF subgroup, N	96	86	75			79
>50% AHI reduction	NA	53% (42% to 64%)	57% (45% to 68%)			NA
AHI	47.1 ± 18.5	25.2 ± 14.2	3.5 ± 6.5			-19.9 (-34.6 to -11.8)
CAI	26.2 ± 17.7	4.1 ± 6.0	3.4 ± 6.9			-26.0 (-40.2 to -14.6)
PGA[b]	NA	58% (NR)	55% (NR)			NA
ESS	8.9 ± 5.1	6.2 ± 4.1	6.1 ± 3.7			-2.0 (-5.0 to 0.0)

AHI: Apnea-Hypopnea Index; CAI: central apnea index; CI: confidence interval; ESS: Epworth Sleepiness Scale; HF: heart failure; IQR; interquartile range; NA: not applicable; NR: not reported; OAI: obstructive apnea index; PGA: Patient Global Assessment.

[a] Patients in the treatment group who had reached 36 months of follow-up prior to study closure.

[b] Patients with marked or moderate improvement in 7-point quality of life scale.

Non-Comparative Studies

Abraham et al. (2015) (11) and Jagielski et al. (2016) (9) presented 6-month and 12-month results from a U.S. Food and Drug Administration regulated feasibility study of 47 patients with CSA of various etiologies who received phrenic nerve stimulation with the remedē system (Table 8). Sleep disorder parameters were measured by polysomnography, through 12 months, with optional sleep testing at 18 months. Quality of life was measured on a 7-point scale, with patients answering the question, "How do you feel today compared with how you felt before having your device implanted?" Central sleep apnea etiologies included HF (79%), other cardiac (13%), and opiate use (4%). Three deaths occurred during the study period, none attributed to the intervention. Five experienced serious adverse events, 3 at the beginning of the study (2 [hematoma, migraine] due to implantation procedure and 1 chest pain), and 2 during 12-months of follow-up (pocket perforation and lead failure). A summary of sleep metric and quality of life results are presented in Table 9.

Wang et al. (2023) conducted a prospective, non-randomized study in a small cohort who was enrolled in the Pivotal Trial. (23) Individuals with CSA with HF (N=9) were enrolled. Comparing pre- and post-treatment there was a reduction in AHI (41 ± 18 e/h vs. 29 ± 25 e/h; p=.02) and increase in mean arterial oxygen saturation (SaO2) (93 ± 1% vs. 95 ± 2%; p=.03). This study was limited because of its small sample size, and it only investigated the effects of treatment over two nights of therapy. Randomized, long-term studies are necessary to better assess the effect of treatment on individuals with CSA and HF.

Table 8. Summary of Non-Comparative Study Characteristics

Study	Country	Participants	Follow-Up
Abraham et al. (2015) (11), and Jagielski et al. (2016) (9)	Germany, Italy, Poland, United States	Adult patients with a history of sleep apnea, predominantly CSA rather than OSA, and an AHI >20 events/hour	12 months (optional 18 months)

AHI: Apnea-Hypopnea Index; CSA: central sleep apnea; OSA: obstructive sleep apnea.

Table 9. Summary of Non-Comparative Study Results (11, 9)

Outcome	Baseline (n=47) mean SD	3 months (n=47) mean SD	6 months (n=41) mean SD	12 months (n=41) mean SD	18 months (n=17) mean SD
AHI, events/hour	49.9 ± 14.6	22.4 ± 13.6	23.8 ± 13.1	27.5 ± 18.3[b]	24.9 ± 13.5[b]
CAI, events/hour	28.0 ± 14.2	4.7 ± 8.6	4.6 ± 7.4	6.0 ± 9.2[b]	4.8 ± 5.8[b]
OAI, events/hour	3.0 ± 2.9	3.9 ± 4.7	3.9 ± 5.4	4.5 ± 6.0	5.6 ± 6.2
4% ODI, events/hour	45.2 ± 18.7	21.6 ± 13.7	23.1 ± 13.1	26.9 ± 18.0[b]	25.2 ± 13.7[b]

Arousal index, events/hour	36.2 ± 18.8	23.7 ± 10.6	25.1 ± 12.5	32.1 ± 15.2	26.8 ± 9.2
QOL, % improvement from baseline[a]	NA	70.8%	75.6%	83.0%	NR

AHI: Apnea-Hypopnea Index; CAI: central apnea index; NA: not applicable; NR: not reported; OAI: obstructive apnea index; ODI: oxygen desaturation index; QOL: quality of life; SD: standard deviation.
[a] Patients with marked or moderate improvement in 7-point quality of life scale.
[b] p<0.006 compared to baseline.

Fox et al. (2017) presented data on the long-term durability of the remedē System, measuring battery lifetime, device exchangeability, lead position stability, and surgical accessibility. (8) Three consecutive patients, mean age 75.7 years, with CSA and HF with preserved ejection fraction were implanted with the remedē phrenic nerve stimulation device due to intolerability of conventional mask therapy. Implantation occurred in 2011 and the patients were followed for 4 years. Mean battery life duration was 4.2 ± 0.2 years. Therapy was well tolerated by the patients, with improvements sustained in AHI, oxygen desaturation index, and quality of life (measured by ESS). Mean device replacement procedure time was 23 minutes, under local anesthesia, with a 2-day hospital stay.

Section Summary: Phrenic Nerve Stimulation for Central Sleep Apnea

Evidence for the use of phrenic nerve stimulation therapy for the treatment of CSA consists of a systematic review, 1 RCT, and observational studies. In the RCT, all patients were implanted with the phrenic nerve stimulation device, with the device activated in the intervention group at 1 month post implantation and activated in the control group at 6 months post implantation. The RCT provided 6-month comparative analyses showing significant improvements in sleep metrics as well as quality of life measures among patients with the activated stimulation device compared with patients receiving the inactivated device. Patients in the activated device arm were followed for 12 months, with analyses showing sustained significant improvements from baseline in sleep metrics and quality of life. A subgroup analysis was conducted on the subgroup of patients with HF, combining 6- and 12-month data from patients in the intervention group and 12 and 18-month data from the control group. Results from the subgroup analysis of patients with HF showed significant improvements in sleep metrics and quality of life at 12 months. An invasive procedure would typically be considered appropriate only if non-surgical treatments had failed, but there is very limited data in which phrenic nerve stimulation was evaluated in patients who had failed the current standard of care, positive airway pressure, or respiratory stimulant medication.

Summary of Evidence

For individuals with central sleep apnea (CSA) who receive phrenic nerve stimulation, the evidence includes a systematic review, 1 randomized controlled trial (RCT), and observational studies. Relevant outcomes are change in disease status, functional outcomes, and quality of life. 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 1 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 quality of life measures. At 12 months follow-up, patients in the activated device arm showed sustained significant improvements from baseline in sleep metrics and quality of life. A subgroup analysis of patients with heart failure combined 6- and 12-month data from patients in the intervention group and 12- and 18-month data from the control group. Results from this subgroup analysis showed significant improvements in sleep metrics and quality of life at 12 months compared with baseline. Results from observational studies supported the results of the RCT. An invasive procedure would typically be considered only if non-surgical treatments had failed, but there is limited data in which phrenic nerve stimulation was evaluated in patients who had failed the current standard of care, positive airway pressure, or respiratory stimulant medication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 the results of a literature review and meta-analysis. (24) 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 a potential for ameliorating central respiratory events, the 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, (25) adjusted the previous guideline, to warn that adaptive servo-ventilation is not recommended for individuals with CSA related to congestive heart failure with an ejection fraction <45%. The use of phrenic nerve stimulation as a treatment option was not addressed in the guideline.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in April 2024 did not identify any ongoing or unpublished trials that would likely influence this policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	33276, 33277, 33278, 33279, 33280, 33281, 33287, 33288, 93150, 93151, 93152, 93153, [Deleted 1/2024: 0424T, 0425T, 0426T, 0427T, 0428T, 0429T, 0430T, 0431T, 0432T, 0433T, 0434T, 0435T, 0436T]
HCPCS Codes	C1823

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
11/15/2024	Document updated with literature review. Coverage unchanged. Added references 3, 5-7, 12, 13, 17-20, 22, and 23.
12/15/2023	Document updated with literature review. Coverage unchanged. No new references added.
08/15/2022	Document updated with literature review. Coverage unchanged. Reference 7 added.
07/01/2021	Reviewed. No changes.
11/01/2020	New medical document. The use of phrenic nerve stimulation for central sleep apnea is considered experimental, investigational and/or unproven in all situations. Coverage is unchanged. This topic was previously addressed on medical policy 706.009 Sleep Related Breathing Disorders: Surgical Management.