Anthem

Medical Policy

Subject: External Upper Limb Stimulation for the Treatment of Tremors
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Description/Scope

This document addresses a wrist-worn external upper limb tremor stimulator of the peripheral nerves. This non-pharmacological/non-surgical treatment option is proposed to aid in the temporary relief of essential tremor (also known as, familial essential tremor or hereditary tremor) of the hand as well as Parkinson's disease.

Please see the following related document for additional information:

- SURG.00026 Deep Brain, Cortical, and Cerebellar Stimulation

Position Statement

Investigational and Not Medically Necessary:

Wrist-worn external upper limb tremor stimulator is considered **investigational and not medically necessary** for all indications, including but not limited to the treatment of essential tremor of the hands and Parkinson's disease.

Rationale

Essential tremor (ET) is the most common neurological disorder among adults and is the most prevalent tremor disorder. The exact mechanisms of ET are not fully understood, however recent studies suggest that ET may be a neurodegenerative disorder.

External upper limb tremor stimulation devices (Cala Trio/Cala kIQ™ [Cala Health, Inc. Burlingame, CA]), are on-demand, non-invasive, wrist-worn devices that deliver individualized electrical stimulation to the nerves of the arm in people with ET. One such device is the Cala Trio Therapy. The proposed action of this device is the delivery of transcutaneous afferent patterned stimulation (TAPS) to the ventral intermediate nucleus thalamus, a key relay point in the central tremor network, and one target of deep brain stimulation (DBS), an invasive treatment of ET. Noninvasive TAPS stimulation to the upper limb using the Cala Trio device is calibrated to an individual's tremor pattern and the user can adjust its strength to account for daily variations in tremor activity. Cala kIQ is the next generation device subsequently developed by the manufacturer to treat action hand tremor for individuals with ET and Parkinson's disease. Cala kIQ is also wrist-worn and utilizes TAPS technology. Cala kIQ is purported to sense an individual's unique tremor and deliver individualized therapy; one therapy session lasts for 40 minutes and sessions may be completed as often as five times daily.

In October 2021, the U.S. Food and Drug Administration (FDA) granted 510k clearance for Cala Trio Therapy with the indication to aid in the temporary relief of hand tremors in the treated hand following stimulation in adults with ET. The device stimulates the nerves in the arm to disrupt the neural signals that cause essential tremor. In November 2022, the FDA granted 510k clearance for the Cala kIQ as a substantially equivalent device. The indications for use are to aid in the temporary relief of hand tremors in the treated hand following stimulation in adults with ET, and to aid in the temporary relief of postural and kinetic hand tremor symptoms that impact activities of daily living in the treated hand following stimulation in adults with Parkinson's disease. Clearance of the Cala kIQ device for Parkinson's disease was based on a single-arm, non-significant risk study that evaluated calibrated therapy in patients with Parkinson's Disease who also had postural hand tremor. A total of 40 individuals were enrolled in the study. Across visits, individuals were assessed using an unvalidated subset of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) dominant hand tasks, and activities of daily living (ADLs) based on an unvalidated subset of Bain and Finley-ADL (BF-ADL) tasks. There were no reports of device-related serious adverse events, and all were resolved with minimal intervention. As noted in the FDA 510(k) Premarket Notification summary:

> These results were descriptive in nature, different patients showed improvement in different tasks tested. None of the patients showed improvement in all of the tasks tested and some of the patients showed no improvement in any of the tasks tested.

There is no data comparing the Cala kIQ device vs. a sham-control device in individuals with Parkinson's disease, and insufficient evidence to assess how the device affects health outcomes.

The predicate device to the Cala Trio and the Cala kIQ was the CalaONE, which obtained De Novo designation from the FDA in May 2017 (DEN170028). According to the De Novo summary document, the CalaONE failed to show a benefit versus placebo (FDA, 2017).The FDA clearance for the Cala Trio therapy was supported by data from the Prospective Study for Symptomatic Relief of ET with Cala Therapy (PROSPECT; NCT03597100), a prospective, post-clearance, multicenter, single-arm, open-label clinical trial evaluating the safety and efficacy of wrist worn TAPS therapy over a 3-month period. Isaacson and colleagues (2020) reported findings for 205 of 263 participants who enrolled in and completed the study. Participants were instructed to use Cala Trio therapy twice daily (in 40-minute sessions) for 3 months, including three in-clinic visits. The co-primary endpoints were clinician-related Tremor Research Essential Tremor Rating Assessment Scale (TETRAS) and patient-rated Bain & Findley Activities of Daily Living (BF-ADL) dominant hand score. Other study measures included "improvement in the tremor power detected by an accelerometer on the therapeutic device, Clinical and Patient Global Impression scores (CGI-I, PGI-I), and Quality of Life in Essential Tremor (QUEST) survey." Eligibility criteria included participants ≥ 22 years of age, a confirmed diagnosis of ET by a movement specialist, a tremor severity score of 2 or above in the dominant hand or arm by any of the TETRAS upper limb items, and a minimum score of 6 across all upper limb items. A BF-ADL score of 3 or more in any one of the upper limb items, a minimum subset score of 8 across all upper limb items, and stable dose of tremor and antidepressant medications were inclusion criteria. Participants were excluded if they had significant alcohol or caffeine consumption within 8 hours prior to the study enrollment, any implanted medical devices or implanted metal in the wrist to be stimulated, presence of other neurodegenerative disease like Parkinson-plus syndrome on neurological exam, suspected idiopathic Parkinson's disease, including presence of parkinsonian features, suspected or diagnosed epilepsy or other seizure disorder, or previous thalamotomy procedure, including stereotactic thalamotomy, gamma knife radiosurgical thalamotomy, and focused ultrasound for the treatment of tremor. The authors reported that the study co-primary endpoints were met ($p<0.00001$),

with 62% (TETRAS) and 68% (BF-ADL) of 'severe' or 'moderate' individuals reported improving to 'mild' or slight'. These results excluded 58 participants that withdrew from the study. There were no serious adverse events reported. Device-related adverse events were reported to have occurred in 18% of participants, with 64% rated mild (itchiness, discomfort), 34% as moderate (electrical burn, significant discomfort), and 2% as severe (1 event, a fall, which was possibly device-related). The study did not find a relationship between concurrent ET medication usage and response to TAPS therapy (66% of participants were on a medication to treat tremor). While initial results look promising for use of TAPs therapy in individuals with ET of the upper extremities the mechanism of therapy remains unclear, and limitations of the study include lack of blinding, absence of a control group (or randomization), and a short duration of follow-up. The authors concluded "future work examining how these clinical trial results translate into the real-world setting would be valuable" and to "establish robust methods to longitudinally maintain a patient blind for peripheral neuromodulation therapies." Two additional manufacturer sponsored clinical trials (NCT05540626, NCT05480215) regarding the Cala Trio device were completed in 2022, however, no results have been published as of the time of this review.

Barath and colleagues (2020) reported an interventional, open-label, single-group study investigating the changes in brain metabolism over 3 months of TAPS use in 5 ET (n=5) participants. Each participant received 40 minutes of TAPS treatment twice daily for 90 days. Brain metabolic activity and tremor severity were measured at baseline, and after 90 days using F-fluorodeoxyglucose (FDG) PET/CT and TETRAS. The participant's tremor power and frequency were measured before and after therapy sessions. Inclusion criteria were ≥ 21 years of age and approved for DBS surgery by the Mayo Clinic DBS Committee for treatment of ET. Participants were excluded if they had alcohol dependence or had an implanted pacemaker, defibrillator, or deep brain stimulator. The mean age of the study participants was 70.2 ± 5.2 years, and the duration of ET ranged from 10 to 57 years (mean 32 ± 16.8 years). Participants enrolled for approximately 89.2 days ± 4.8 days and completed 136.2 ± 41.3 TAPS sessions; participant compliance was 77.3 ± 25.6 %. The FDG PET/CT results demonstrated areas of increased metabolism in the ipsilateral cerebellar hemisphere and decreased metabolism in the contralateral hemisphere following 90 days of therapy, compared to day 1 ($p<0.05$). Comparison of pre- and post-therapy measurements over 90 days showed decreased tremor power ($p<0.0001$), but no change in frequency. The day 1 TETRAS scores decreased from 6.5 to 4.1 following TAPS ($p=0.05$). The 90-day pre- and post-TETRAS scores also decreased from 4.9 to 4.1 ($p=0.14$ and $p=0.05$, respectively). No adverse events were reported. The authors concluded that longitudinal TAPS of the median and radial nerves affect brain metabolism in areas necessary for motor coordination which may cause ET. Study limitations included its small study population and weak power. Additional studies with robust methodology and power are needed to further elucidate the clinical mechanism of TAPS.

Yu and colleagues (2020) reported a single-arm, open-label study, of 15 individuals with ET who received TAPS therapy. The aim was to evaluate the duration of tremor reduction. Inclusion criteria were individuals 22 years of age and older diagnosed with ET by an internist or neurologist. Participants performed four hand tremor-specific tasks (postural hold, spiral drawing, finger-to-nose reach, and pouring) from the Fahn-Tolosa-Marin Clinical Rating Scale (FTM-CRS) prior to, during, and 0, 30, and 60 minutes following TAPS therapy. Tremor severity was rated using the FTM-CRS, and simultaneously with wrist-worn accelerometers. The duration of tremor reduction was measured by improvement in the mean FTM-CRS score across all four tasks compared to baseline, and reduction in accelerometer-measured tremor power compared to baseline for each task. The results demonstrated that mean FTM-CRS scores improved for at least 60 minutes beyond the end of TAPS for 80% of participants. For the assessed tasks, tremor power improved for at least 60 minutes beyond the end of TAPS for over 70% of participants. The postural hold task had the most significant reduction in tremor power (median 5.9-fold peak reduction in tremor power) and had at least 60 minutes of improvement relative to baseline beyond the end of TAPS therapy for 73% of participants. No adverse events were reported. The authors concluded that tremor power is a valid, objective assessment metric, and that TAPS therapy may improve upper limb tremor symptoms for at least 1 hour post therapy which may improve ability to perform ADL's in individuals with ET. The authors also noted that 5 of the 15 subjects in this study who were on pharmacologic treatment for ET, may have ingested medication that could have influenced the duration of effect. The NIH considers TETRAS the superior ET assessment measure compared to FTM, stating "TETRAS has two main advantages over FTM in the assessment of tremor severity: (1) the absence of a ceiling effect in patients with severe ET, and (2) the inclusion of wing-beating tremor" (2017). While the results of this study are promising, larger cohorts with similar ET tremor scales are needed to further evaluate the clinical utility of TAPS. The American Academy of Neurology (AAN) has an evidence-based guideline update for the treatment of essential tremor that was last reaffirmed July 2017 (Zesiewicz, 2017). This document includes recommendations for pharmacologic agents and surgical interventions for individuals with ET. No recommendations for use of external upper limb tremor stimulator device as a treatment of ET are provided.

The International Essential Tremor Foundation's (IETF) Essential Tremor in Adult Patients Guideline Advisory document (2021) recognizes Cala Trio therapy as a "non-pharmacological/non-surgical treatment option" in combination with first-line pharmacological approaches (propranolol, primidone), or prior to or in conjunction with second- or third-line pharmacotherapies (topiramate, gabapentin, other beta blockers, or benzodiazepines). However, the recommendations based on expert consensus for Cala Trio therapy are not supported by any evidence-based explanation.

In summary, the available evidence in peer-reviewed medical literature is insufficient to evaluate the effect of TAPS therapy with Cala Trio on health outcomes in individuals with ET. Additional evidence in the form of well-designed and conducted studies measuring longer follow-up times are needed to evaluate the clinical utility of this treatment approach.

Background/Overview

According to the National Organization for Rare Disorders (NORD) rare disease database for essential tremor, nearly 7 million Americans are currently diagnosed with ET. The incidence of ET increases with age and more than 4% of individuals over age 40 have ET (NORD, 2022). The National Institute of Neurological Disorders and Stroke (NINDS) considers ET a chronic, progressive, and disabling neurological disease that causes uncontrolled rhythmic shaking. It is characterized by the presence of an action tremor (shaking during voluntary muscle movements), most often the hands or arms. In individuals with ET, other motor symptoms may be present including an unsteady manner of walking due to an inability to coordinate voluntary movements (ataxia), and in some cases, a variety of non-motor symptoms including cognitive impairment, depression or anxiety may develop. Population-based studies in the U.S. estimate that 2.2% of the U.S. population suffers from ET, and although most common among the elderly, the prevalence is increasing across age groups. Individuals with ET have higher rates of anxiety and depression than the general population, and difficulties with normal daily activities can potentially dramatically impact quality of life (NINDS, 2022).

There is no cure for ET and only a handful of pharmacologic or surgical treatments exist to help individuals manage their symptoms. First-line treatment consists of pharmacotherapies, such as propranolol and primidone. Second and third-line pharmacological approaches include topiramate, gabapentin, other beta-blockers, or benzodiazepines. However, response to pharmacotherapies varies, and high doses are often required for effective tremor reduction, increasing the burden of side effects for individuals and reducing tolerability and compliance. Deep brain stimulation surgery and magnetic resonance imaging (MRI)-guided focused ultrasound ablation are additional treatment options for tremor. However, not all individuals are appropriate candidates for such surgical procedures.

Definitions

Essential tremor (ET): A chronic, incurable condition with unknown cause characterized by involuntary, rhythmic movement of a body part, most typically the hands and arms.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

HCPCS

A4542	Supplies and accessories for external upper limb tremor stimulator of the peripheral nerves of the wrist
E0734	External upper limb tremor stimulator of the peripheral nerves of the wrist

ICD-10 Diagnosis

	All diagnoses

References

Peer Reviewed Publications:

1. Barath AS, Rusheen AE, Min HK, et al. Brain metabolic changes with longitudinal transcutaneous afferent patterned stimulation in essential tremor subjects. Tremor Other Hyperkinet Mov (N Y). 2020; 10(1):52.
2. Isaacson SH, Peckham E, Tse W, et al. Prospective home-use study on non-invasive neuromodulation therapy for essential tremor. Tremor Other Hyperkinet Mov (N Y). 2020; 10(1):29, 1-16.
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4. Pahwa R, Dhall R, Ostrem J, et al. An acute randomized controlled trial of noninvasive peripheral nerve stimulation in essential tremor. Neuromodulation. 2019; 22:537-545.
5. Yu JY, Rajagopal A, Syrkin-Nikolau J, et al. Transcutaneous Afferent Patterned Stimulation (TAPS) therapy reduces hand tremor for one hour in essential tremor patients. Front. Neurosci. 2020; 14:530300.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Cala Health, Inc. Prospective Study for Symptomatic Relief of ET with Cala Therapy (PROSPECT). NLM Identifier: NCT03597100. Last updated July 23, 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT03597100. Accessed on June 23, 2023.
2. International Essential Tremor Foundation Consensus and Physician Experts. Essential tremor in adult patients. Available at: https://www.guidelinecentral.com/guideline/502775/. Accessed on June 23, 2023.
3. U.S Food and Drug Administration (FDA). 510k Summary. K2032088. Cala Health, Inc. Cala Trio. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf20/K203288.pdf. Accessed on June 23, 2023.
4. U.S Food and Drug Administration (FDA). 510k Summary. K222237. Cala Health, Inc. Cala kIQ. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf22/K222237.pdf. Accessed on June 27, 2023.
5. Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: Treatment of essential tremor. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Last reaffirmed on July 29, 2017. Available at: https://neurology.org/content/77/19/1752. Accessed on June 23, 2023.

Websites for Additional Information

1. National Institute of Neurological Disorders and Stroke. Tremor fact sheet. Last reviewed June 7, 2023. Available at: https://www.ninds.nih.gov/health-information/disorders/essential-tremor?search-term=essential%20tremor%20fact%20sheet. Accessed on June 23, 2023.
2. National Library of Medicine. Medical Encyclopedia. Essential tremor. Available at: https://medlineplus.gov/ency/article/000762.htm#:~:text=Essential%20tremor%20(ET)%20is%20a,stop%20the%20shaking%20at%20will. Accessed on June 23, 2023.
3. National Library of Medicine. Journal list. Ondo W, Hashem V, LeWitt PA, et al. Comparison of the Fahn-Tolosa-Marin Clinical Rating Scale and the Essential Tremor Rating Assessment Scale. Mov Disord Clin Pract. 2017 23;5(1):60-65. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6174461/. Accessed on June 28, 2023.
4. National Organization for Rare Disorders. Rare disease database. Essential tremor. Available athttps://rarediseases.org/?s=essential+tremor&rdb-search=true&post_type%5B%5D=rare-diseases&post_type%5B%5D=gard-rare-disease. Accessed on June 23, 2023.

Index

Cala Trio
External upper limb tremor stimulator

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
	12/28/2023	Updated Coding section with 01/01/2024 HCPCS changes, added A4542, E0734 replacing K1018, K1019 deleted as of 01/01/2024.

Revised	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised Description/Scope to include indication for Parkinson's Disease. Revised Position Statement to include INV NMN for Parkinson's. Updated Discussion, References, and Website sections.
	03/29/2023	Updated Coding section with 04/01/2023 HCPCS changes, descriptor revision for K1019.
New	08/11/2022	MPTAC review. Initial document development.

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