



Utilization Management Policy

Calmare® Pain Therapy Treatment

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Policy Statement

Optum* by OptumHealth Care Solutions, LLC considers Calmare® Pain Therapy Treatment to be unproven and not medically necessary due to insufficient scientific evidence of efficacy for the treatment of noncancer-related neuropathic pain disorders.

Use of the Calmare (Scrambler) pain therapy for the treatment of noncancer-related neuropathic pain is supported by some preliminary positive published information regarding safety and/or efficacy. However; a beneficial impact on health outcomes e.g., durable pain reduction and improved function have not been proven because the data are sparse and the evidence is of very low quality.

Purpose

This policy has been developed as the clinical criterion that describes the position of Optum regarding the efficacy, effectiveness, risks and burdens associated with the use of Calmare® Pain Therapy Treatment (Scrambler Therapy) for the treatment of noncancer-related neuropathic pain.

Key Policy Question

Is there sufficient research evidence of a beneficial impact on health outcomes (efficacy and safety) of Calmare pain therapy, either as a single or combined therapy, for the sustained reduction of pain and disability to conclude this intervention is an appropriate therapeutic approach for patients diagnosed as having noncancer-related neuropathic pain?

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Summary

- Calmare (‘scrambler’) pain therapy treatment is currently being investigated for use in the treatment of individuals having either oncological (cancer related) or noncancer related neuropathic pain.
- To date, only 2 studies have included patients diagnosed with noncancer-related neuropathic pain
- There were no studies identified that investigated the long-term effect of Calmare therapy on pain and no studies appear to have evaluated functional/disability-related outcomes.
- The clinical evidence is not sufficient to permit conclusions about the benefits of Calmare (scrambler) therapy as a treatment of patients with noncancer-related neuropathic pain.
- There were no clinical practice guidelines identified where Calmare therapy was evaluated for appropriateness in the treatment of patients with noncancer-related neuropathic pain
- Other health care organizations that have policies regarding Calmare therapy for pain treatment have concluded the service is investigational and noncovered.
- Further research is very likely to have an important impact on confidence in the estimate of effect.

Scope

The application of this policy is limited to services involving a cutaneous electrostimulation device best described as Calmare[®] Pain Therapy Treatment (Calmare) including Scrambler Technology and MC5-A for the treatment of neuropathic pain due to underlying noncancer-related disorders. Excluded from the scope of this policy is the application of Calmare for cancer-related neuropathic pain including but not limited to chemotherapy-induced peripheral neuropathy.

Description

The Calmare MC-5A device uses a 5-channel multi-processor that is able to simultaneously treat multiple pain areas by applying surface electrodes to the skin. The device then sends a very low current of electrical stimulation to generate a patient-specific cutaneous electrostimulation

The Calmare device reportedly differs from other electrical nerve stimulation technologies e.g., transcutaneous nerve stimulation (TENS). TENS units employ a singular current, while Calmare has 16 different algorithms. Reportedly, there is no accommodation or development of a tolerance to the device as the machine does not repeat any sequence during the treatment.

Background

Introduction

Calmare[®] Pain Therapy Treatment (Calmare) is a U.S. FDA 510(k)-cleared (February 2009) and European CE mark-certified pain therapy medical device for the non-invasive treatment of chronic neuropathic and oncologic pain. The device, which employs a biophysical “scrambler” technology rather than a biochemical approach, reportedly creates and sends a “no-pain” signal which becomes the dominant signal received by the brain – thus overriding the pain signal and providing relief for the patient [Calmare website].

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The Calmare medical device was developed by Professor Giuseppe Marineo, a researcher and bioengineer, and the founder and manager of Delta Research & Development. Delta R&D is the Bioengineering Research Centre affiliated with Tor Vergata University of Rome, Italy.

The technology is sponsored by Competitive Technologies, Inc. (OTCQX: CTTC) through the efforts of Prof. Giancarlo Elia Valori of the Italian business development group, Sviluppo Lazio S.p.A. CTTC licensee GEOMC of Korea is manufacturing the device commercially for worldwide sales [Competitive Technologies, Inc. website].

According to the CTTC (<http://www.calmarett.com/about/index.html>), “Calmare has successfully treated over 4,000 patients worldwide, where it has been shown to be effective in treating neuropathic and oncologic pain.” Conditions treated include:

- Chemotherapy-induced peripheral neuropathy (CIPN)
- Phantom limb syndrome
- Sciatica
- Post-surgical neuropathic pain
- Low back pain
- Neck pain
- Reflex sympathetic dystrophy
- Postherpetic neuralgia (PHN)

Clinical trials investigating Calmare therapy are in-progress in the USA at Virginia Commonwealth University (Massey Cancer Center), the University of Wisconsin-Madison (Paul Carbone Cancer Center) and the Mayo Clinic.

Three-day programs that provide primary training in the application of Calmare therapy are held at public hospitals in Rome directly by Prof. Giuseppe Marineo. The training course is for clinical researchers and physicians that will themselves become trainers in their country of origin. Apart from addressing issues pertaining to the correct methodology usage, training clarifies scientific and methodology issues on clinical research [Scrambler Therapy website].

Clinical Application

Patient Selection

The CTTC website (<http://www.calmarett.com/pain/whoitsfor.html#panelid=indications>) lists indications, contraindications and precautions to guide judgments about the appropriateness of Calmare pain therapy treatment for specific patients.

1. Indications:

- Chemotherapy-induced Peripheral Neuropathy (CIPN)
- Chronic Cancer Pain
- Failed Back Surgery Syndrome (FBSS)
- Sciatic and Lumbar Pain
- Phantom Limb Syndrome
- Postherpetic Neuralgia (PHN)
- Post-surgical Neuropathic Pain
- Brachial Plexus Neuropathy
- Low Back Pain (LBP)
- Chronic Neuropathic Pain

2. Contraindications:

- pacemaker or automatic defibrillator
- aneurysm clip, vena cava clips, or skull plates (metal implants for orthopedic repair, e.g. pins, plates, joint replacements are allowed)
- pregnant and/or breastfeeding

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- history of epilepsy, brain damage, use of anti-convulsants other than pain control
- prior celiac plexus block, or other neurolytic pain control treatment, within 4 weeks
- wounds or skin irritation in areas where the electrodes are required to be placed
- history of, or have been treated for myocardial infarction or ischemic heart disease with the past six months
- severe arrhythmia or any form of equivalent heart disease
- implanted drug delivery system
- active withdrawal from drugs and/or alcohol
- previous intolerance to transcutaneous electronic nerve stimulation
- latex allergies

3. Precautions:

- pain originating in the central nervous system
- stimulation over the neck (laryngeal and pharyngeal) due to muscle contractions may be strong enough to close the airway or cause difficulty in breathing
- because this device is capable of delivering a charge per pulse of 25 micro coulombs or greater, electrodes should not be placed in a trans-thoracic position (may cause cardiac arrhythmia)
- patients who are prone to skin irritation (isolated cases have occurred)
- uncertain diagnosis of neuropathic pain
- an implanted pain stimulator (operating or nonoperational) in which the proposed treatment is in the area of the implanted device (electrical current to area may interfere with the operation of the implanted device)
- patients that are connected to other electronic monitoring equipment (ECG monitor) - may not operate properly with the medical device is in use
- patient is taking neuroleptic medications (examples: carbamazepine, pregabalin, gabapentin) which appear to "interfere with treatment efficacy" and "decrease longevity" of no-pain post treatment protocol

Treatment Protocol

The CTTC website outlines the protocol, "Patients receive a prescription from their doctor to receive treatments as an outpatient procedure. Each treatment steadily diminishes the pain intensity of the patient. During treatment, a patient is treated at a level that removes pain and doesn't cause discomfort."

- For patients with neuropathic pain: 10-12 daily treatments of 30-45 minutes are scheduled during which the patient is connected to the device.
- For patients with oncologic pain: 10-12 treatments are scheduled based on the patient's pain control needs."

The same website provides more detailed guidance:

Recommended Treatment Protocol
<http://www.calmarett.com/media/pdf/Treatment%20Protocol.pdf>
 (March 2009)

The Calmare Therapy Treatment for pain relief has been specifically designed and clinically tested to provide treatment of high-intensity neuropathic and oncologic pain, including pain resistant to morphine and other drugs. Patients selected for treatment typically have not responded satisfactorily to any previous treatment protocol performed in accordance with Multidrug Therapy (MDT), or surface electrostimulation.

Treatment Protocol

- To guarantee the most effective and lasting pain relief, treatment should last 45 minutes, but it is possible to set up from 20 to 60 minutes.
- The treatment program should include individual treatment sessions, that can be repeated, made up of at least 10 to 12 treatments, to be carried out at a frequency of five times a week (one treatment per day).
- The electrodes are never applied directly on the pain area.
- Electrodes are applied on the dermatomes, which correspond to one/two superior metameres, and one/two inferior metameres at the widest extension in the pain affected area.
- The intensity of the electric stimulus used to modulate and transmit the system's non-pain information will vary from patient to patient.
- Patient adaptation to the intensity of the treatment should be achieved on the basis of the criterion of the maximum intensity individually bearable by the patient without any input of pain or discomfort.
- The patient should be treated only when the disappearance of the pain during the application is immediate and complete. This is a clear sign that the proper nerve pathway has (have) been correctly identified, or, even in the case of partial success no feeling of discomfort is reported by the patient.
- If the clinician is unable to identify patient's dermatometric pathways of use in a correct therapeutic approach a relapse of pain will probably occur during treatment of the symptoms.
- In the case of polyneuropathies any medium-term relapse may be effectively corrected by initiating another treatment cycle.

Exclusion Criteria
 The following exclusion criteria are recommended when considering a patient for treatment:

- Pacemaker user
- Neurolithic blockage of celiac plexus
- Other Neurolesive pain control treatment
- Anticonvulsant drugs

The CTTC website also includes protocols tailored for neuropathic pain conditions and oncologic pain:

| NEUROPATHIC PAIN INDICATIONS | | TREATMENT PROTOCOL |
|---|--|--|
| <ul style="list-style-type: none"> ○ Post-Surgical Neuropathic Pain (PSNP) ○ Post-Herpetic Neuralgia (Sciatic and Lumbar Pain) ○ Narrow Canal Syndrome SCS (Putative neuropathic pain) ○ Failed Back Surgery Syndrome (FBSS) ○ Trigeminal Neuralgia ○ Pudendal Neuropathy Brachial Plexus ○ Neuropathy Low Back Pain ○ Phantom Limb Pain Syndrome | | <ul style="list-style-type: none"> – Establish initial treatment program at 10 to 12 individual treatment sessions. – Treatment should be set at a frequency of one treatment per day. – Set treatment duration to 30 to 45 minutes. – Determine proper level of intensity to achieve maximum allowed without discomfort to patient. – Patient should be void of pain and discomfort during treatment. – Follow procedures in User Manual. |
| ONCOLOGIC PAIN INDICATIONS | | TREATMENT PROTOCOL |
| Cancers: | | <ul style="list-style-type: none"> – Establish initial treatment program at 10 to 12 individual treatment sessions. – Frequency of treatment is dependent upon patient's need for analgesia. – Set treatment duration to 45 minutes. – Determine proper level of intensity to achieve maximum allowed without discomfort to patient. – Patient should be void of pain and discomfort during treatment. – Follow procedures in User Manual. |
| <ul style="list-style-type: none"> ○ Pancreatic ○ Gastric ○ Colon ○ Ovarian ○ Cervical ○ Lung ○ Colorectal ○ Prostate | <ul style="list-style-type: none"> ○ Rectal ○ Uterine ○ Bladder ○ Kidney ○ Liver ○ Gall Bladder ○ Laryngeal ○ Esophageal | |

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Literature Review

Search Strategy

A structured literature search and qualitative review using a broadly adopted appraisal methodology, Grading of Recommendations Assessment, Development and Evaluation (GRADE), was conducted by a clinical work group [Furlan, GRADE]. Biomedical databases and consumer-oriented search engines were used to identify and retrieve relevant evidence. Hand-searches of bibliographies and non-indexed documents were included in the search strategy. Additionally, the Competitive Technologies, Inc. (CTTC) website and the Scrambler Therapy official scientific and clinical information site (ST-NET) were searched for research evidence. Research in-progress and protocols were identified by searching www.clinicaltrials.gov. Authors were contacted to obtain additional information.

Evidence Extraction

No systematic literature reviews were identified. The literature search did identify five published studies describing the effects of Calmare pain therapy treatment. [Marineo (2012), Sabato, Smith, Marineo (2003a), Marineo (2003b)]. The application of Calmare therapy for noncancer-related neuropathic pain was investigated in 2 studies [Sabato, Marineo (2012)]. A single small randomized clinical trial (RCT) [Marineo, 2012] and a single case series [Sabato] were subjected to formal quality appraisal. [Table 1] Disorders associated with noncancer-related neuropathic pain for which Calmare was investigated included spinal canal stenosis, sciatic and lumbar radiculopathy, brachial plexus lesions, low back pain, trigeminal neuralgia, pudendal neuropathy, post-surgical neuropathy, and post-herpetic neuralgia. In addition to three case series [Smith, Marineo (2003a), Marineo (2003b)] that investigated solely oncologic pain, case reports, physiologic (lab) studies, opinion papers, and studies where only the abstract was accessible were not included in the formal quality appraisal. [Table 2]

Evidence Appraisal

The two appraised studies were rated “low” and “very low” for answering the key policy question. None of the identified studies assessed for the patient-important outcomes of function or disability. There was uncertainty about the results concerning ‘pain’ – due mainly to imprecision (only a single study for each important outcome that was measured, small sample size, and absence of interval estimation e.g., confidence intervals), and to the lack of reporting of long-term follow-up. Other factors contributing to the low/very low quality ratings included the risk of selection bias and indirectness concerning the study population. [Table 3]

Marineo (2012) conducted a pilot randomized clinical trial that included 52 patients. Of these, 8 patients were diagnosed with spine-related neuropathic pain due to stenosis. Another 16 patients had post-herpetic neuralgia. Twenty-eight patients were categorized as having post-surgical pain. “Scrambler” (Calmare) therapy was compared to guideline-based drug management. All patients diagnosed as having noncancer-related neuropathy demonstrated statistically and clinically significant results favoring Calmare therapy at 1, 2 and 3 months follow-up.

Confidence in the conclusions from this trial was rated as low for short-term pain reduction and very low for intermediate pain outcomes. Imprecision (only one study for the outcome, confidence intervals were not reported for the diagnostic groups, and the small number of subjects within the study [N=52]), and indirectness (the results from discrete populations eg, spinal stenosis may not apply to other causes of noncancer-related neuropathic pain) were the primary reasons for reduced quality ratings. Additionally, there were a number of methodological limitations. The randomization scheme – assigned in consecutive order – did not provide true randomization. Allocation was not concealed. Blinding did not reportedly take place at any point in the trial. [Appendix 1]

The assessment of the magnitude of treatment effects was calculated as standardized effect size measures (r). A large effect (0.84), which elevated confidence in the appraisal of results, was reported for short-term pain reduction. A medium effect (0.61) was recorded at 3 months follow-up. Other measures of relative effect eg, relative risk (RR) could not be calculated without individual participant data eg, event rates. This information was requested from the study authors but was not available.

In a case series study design, where visual analog scale (VAS) ratings of pain intensity were obtained before and after each treatment session, Sabato, et al. reported on 226 patients suffering from intense drug-resistant neuropathic pain. In this sample, there were 180 patients with specific diagnoses describing noncancer-related disorders as well as another 46 individuals categorized as having ‘other’ neuropathies. The trends reported for pre and post session VAS (pain intensity) scores demonstrated statistical and clinically significant results favoring Calmare therapy. Other measures e.g., stratification by response category did not report on findings by diagnosis.

Confidence in the results of the study is limited by the design (nonexperimental), uncertainty about the directness of the study (e.g., limited patient data, description of diagnostic criteria, incomplete patient important outcomes e.g., disability and health-related quality of life), uncertainty about the precision of the study e.g., the absence of interval estimates (confidence intervals) and small sample size. [Appendix 2]

In addition to published studies, there are at least 6 trials at varying stages of progress. [Table 4] Five of these studies seek to investigate Calmare pain therapy treatment for oncological neuropathic pain. One study is planned to explore whether post-herpetic neuralgia (PHN) pain can be decreased with scrambler (Calmare) therapy.

Research Evidence Rating

The ratings based upon the formal appraisal of research evidence concerning disorders associated with noncancer-related neuropathic pain are as follows:

Low back pain, brachial plexus pain, spinal canal stenosis, sciatic and lumbar radiculopathy, failed back surgery, trigeminal neuralgia, pudendal neuropathy, post-surgical neuropathy, and post-herpetic neuralgia:

| | | |
|---|--------------------------------|---|
| C | Potential but Unproven Benefit | Use of Calmare® (scrambler) pain therapy treatment is supported by some positive published data regarding safety and/or efficacy for neuropathic pain associated with the above disorders, but a beneficial impact on health outcomes has not been proven for the following reason: the clinical evidence is imprecise and the quality of evidence is very low. |
|---|--------------------------------|---|

Other noncancer-related disorders:

| | | |
|---|-------------------|---|
| D | No Proven Benefit | The research regarding the use of Calmare® (scrambler) pain therapy for the treatment of other noncancer-related disorders is so limited that an appraisal of safety and efficacy cannot be made. |
|---|-------------------|---|

Additional Considerations

The application of a structured decision making framework has been promoted to support policy making, when experimental clinical research evidence is insufficient for making confident judgments. [Hayes, Sutcliffe]. The following series of questions comprise a qualitative assessment that relies on pragmatic reasoning [Hayes]:

Pragmatic Judgments

1. Does Calmare therapy address a significant patient or plan need?
 - ~4 million people in the USA suffer from neuropathic pain [Galluzzi]
 - 88% of neuropathic pain is noncancer-related [Galluzzi]
 - Estimates suggest that between 20 and 35% of patients with low back pain (LBP) may have an underlying neuropathic component [Baron].
 - There are more established options [Attal, Chou, Cutler, NICE, O'Connor, TOP] for most noncancer-related neuropathic pain disorders where Calmare therapy has been studied and/or recommended
 - However, approximately 50% of individuals studied in clinical trials fail to experience clinically meaningful pain relief with pharmacotherapy [Dworkin (2010)].
 - Specific patient sub-groups most likely to benefit from Calmare therapy have not been established
2. Is insufficient evidence likely to continue?
 - There is limited research taking place concerning the use of Calmare therapy for noncancer-related neuropathic pain.
 - The National Institutes of Health website notes there are at least 6 clinical trials involving Calmare therapy that are in development [Clinical Trials Registry].
 - The Scrambler Therapy official scientific and clinical information site (ST-NET) serves as a portal to standardize and advance trials investigating Calmare therapy.
3. Is Calmare therapy already used or will it soon be in widespread use?
 - There are a total of 17 certified Calmare[®] Pain Therapy Treatment locations in the USA listed on the CTTC website (<http://www.calmarett.com/locations.html#panelid=Northeast>)
4. Do the potential benefits for the patient outweigh the risks?
 - The current evidence does not allow for a confident assessment of treatment effects for patient-important outcomes
 - The risk of adverse events appears to be very low, when the patient selection criteria described in published studies are respected.

What are the Conclusions of Others?

The literature search and review did not identify any clinical practice guidelines describing a position on the appropriateness of Calmare (Scrambler) pain therapy treatment for noncancer-related neuropathic pain [Bril, Chou, Dworkin (2007, 2010), Hooten, O'Connor, Savigy, TOP]. Evidence-based 'point-of-care' summaries either do not comment on Calmare therapy [DynaMed] or conclude that additional trials are warranted [Up-To-Date].

Some health care organizations have published policies commenting on Calmare pain therapy treatment – and have determined the technology is investigational for the treatment of any type of pain, and not a covered service [Regence, Humana].

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- Appendix 1: Risk of Bias (limitations in study design or implementation) – Marineo**
- Appendix 2: Risk of Bias (limitations in study design or implementation) – Sabato**

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Table 1: Clinical Studies Meeting Selection Criteria for Quality Appraisal

| Author Date | Study Design | Population and Setting | Interventions & Schedule | Outcome Variables | Follow-up Assessments | Results |
|----------------|---|--|---|---|--|---|
| Marineo (2012) | Randomized Controlled Trial (pilot study) | <ul style="list-style-type: none"> N = 52 adults diagnosed as having chronic noncancer-related neuropathic pain Refractory to previous pharmacotherapy (antidepressants, anticonvulsants, opioids) and TENS Categorized as: <ul style="list-style-type: none"> Post-surgical (28) Post-herpetic neuralgia (16) Spinal canal stenosis (8) Outpatient pain center | Intervention group (N=26): <ul style="list-style-type: none"> Scrambler therapy for a cycle of 10 daily sessions Continue with prior medications Control group (N=26): <ul style="list-style-type: none"> New pharmacotherapies: <ul style="list-style-type: none"> Amitriptyline Clonazepam Oxycodone | <ul style="list-style-type: none"> VAS | <ul style="list-style-type: none"> 1-month (from entry) 2-months 3-months | <ul style="list-style-type: none"> Both groups demonstrated clinically significant improvement in pain intensity at 1-month follow-up. The magnitude of improvement was significantly greater in the intervention group at all follow-up assessments; however, there was a narrowing of the difference between groups over time Subgroup analyses for patients having specific diagnoses showed similar within and between group trends. There were no adverse events observed with the use of Scrambler therapy. |
| Sabato (2005) | Case Series | <ul style="list-style-type: none"> N = 226 adults with noncancer-related neuropathic pain: <ul style="list-style-type: none"> Failed back surgery (45) Lumbar radiculopathy (33) Post herpetic neuralgia (21) Post-surgery nerve lesion neuropathy (21) Trigeminal neuralgia (20) Low back pain (14) Brachial plexus neuropathy (12) Pudendal neuropathy (11) Other neuropathies (46) Refractory to pharmacotherapy Setting not described | <ul style="list-style-type: none"> 1–6 daily therapy sessions (cycles) 5 treatments per session 30 minutes per treatment | <ul style="list-style-type: none"> VAS | <ul style="list-style-type: none"> Immediately after each session | <ul style="list-style-type: none"> Globally: <ul style="list-style-type: none"> 80.9% of subjects were classified as responders (>50% pain relief) 10.18% were partial responders (25–49% pain relief) 9.73% were non-responders (<24% pain relief or VAS >3) Noncancer-related neuropathic pain groups: <ul style="list-style-type: none"> Failed back surgery = 60% pain relief Lumbar/sciatic pain = 69.3% Brachial plexus pain = 66.7% Low back pain = 59.6% Post herpetic neuralgia = 58% Post surgical neuropathy = 67% Trigeminal neuralgia = 69.6% Pudendal neuropathy = 56% Other neuropathies = not reported No undesirable side-effects reported |

Legend: VAS = visual analog scale

Table 2: Reasons for Studies Excluded From Quality Appraisal

| Study/Source | Reason |
|--|---|
| Case reports | Do not meet the minimum criteria for evidence profiling |
| News releases/articles/advertisements | Do not meet the minimum criteria for evidence profiling |
| Commentaries/presentations/opinion articles | Do not meet the minimum criteria for evidence profiling |
| Citations that did not yield any search results | Unable to retrieve study as cited |
| Citations that yielded only abstracts | Unable to retrieve full text |
| Basic science research | Clinical application yet to be established |
| Studies not published in English | Unable to translate |
| Studies investigating populations without identified noncancer-related neuropathic pain e.g., oncologic pain | Out-of-scope |

Utilization Management Policy

Table 3: Quality Assessment & Summary of Findings by Important and Critical Outcomes

Key Question: *Is there sufficient research evidence of a beneficial impact on health outcomes (efficacy and safety) of Calmare pain therapy, either as a single or combined therapy, for the sustained reduction of pain and disability to conclude this intervention is an appropriate therapeutic approach for patients diagnosed as having noncancer-related neuropathic pain?*

Critical Outcome Variables: Pain and Disability

| Quality Assessment | | | | | | | Summary of Findings | | | | Quality |
|---|-------------|-----------------------|---------------|-----------------------|-----------------------|--|-----------------------|----------------|--------------------------------|--|-----------------|
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other Considerations (AE reporting, publication bias, dose-response) | No. of Patients | | Effect [A] | | |
| | | | | | | | Intervention: Calmare | Control: Meds. | Relative Benefit (Effect Size) | Absolute Benefit: Points on VAS (% Change) | |
| Pain intensity – Immediate follow-up (after each treatment) | | | | | | | MCIC = 2.0 cm | | | | |
| 1 | Case Series | High risk of bias [B] | N/A | Indirectness -2 [C] | Imprecise data -2 [D] | No events | N = 226 | N/A | N/A | - FBS: 4.22 - LR: 3.91 - BP: 4.83 - LBP: 3.77 - PHN: 3.72 - PSN: 4.74 - PN: 3.82 - TN: 4.32 | Very Low |
| Pain intensity – Short-term follow-up (1-month after randomization; range of scores: better indicated by less) | | | | | | | MCIC = 2.0 cm | | | | |
| 1 | RCT | Low risk of bias | N/A | Some indirectness [E] | Imprecise data -2 [D] | No events | N = 26 | N = 26 | Calmare: -5.0 (0.84) [F] | Control: -2.3 (28%) Intervention: -7.23 (90%) | Low |
| Pain intensity – Intermediate-term follow-up (3-months after randomization; range of scores: better indicated by less) | | | | | | | MCIC = 2.0 cm | | | | |
| 1 | RCT | Low risk of bias | N/A | Some indirectness [E] | Imprecise data -2 [D] | No events | N = 26 | N = 26 | Calmare: -3.8 (0.61) | Control: -2.2 (27%) Intervention: -5.98 (74.6%) | Very Low |

- A. Effect measures were limited to mean changes in VAS scale scores and mean percentile changes. Standardized effect size measures could not be calculated without individual participant data and/or standard deviations
- B. High risk of selection bias due to incomplete reporting of the inclusion criteria, uncertainty about the enrollment process and timeframe of participant selection (confidence in results decreased by 1)
- C. Indirectness due to limited patient data, no description of diagnostic criteria, and incomplete patient important outcomes e.g., disability and health-related quality of life (confidence in results decreased by 2)
- D. There is only one study for the outcome; Optimal information size criterion not met; CI not reported for diagnostic groups (confidence in results decreased by 2)
- E. Discrete populations (SCS, PHN, PSN) studied. Results may not apply to other causes of noncancer-related neuropathic pain (confidence in results decreased by 1)
- F. Large effect size (increase confidence in results by 1)

Key: AE – adverse events; SCS – spinal canal stenosis; VAS – visual analog scale; N/A – not applicable; FBS – failed back surgery; LR – lumbar radiculopathy; BP – brachial plexus disorders; LBP – low back pain; PHN – post herpetic neuralgia; PSN – post surgical neuropathy; PN – pudendal neuropathy; TN – trigeminal neuralgia; RCT – randomized controlled trial; NC – not calculated data not available; Quality –high, moderate, low, or very low; CI – confidence interval

Table 4: Trials In-Progress

| |
|--|
| <ul style="list-style-type: none">• Scrambler Therapy in Treating Chronic Pain in Patients With Rash From Varicella Zoster Virus Infection<ul style="list-style-type: none">○ NCT ID: NCT01347736○ Sponsor: Mayo Clinic○ Principal Investigator: Charles L. Loprinzi○ Protocol IDs: MC10CE, NCI-2011-00338• Scrambler Therapy in Treating Pain and Peripheral Neuropathy in Patients Previously Treated With Chemotherapy<ul style="list-style-type: none">○ NCT ID: NCT01347723○ Sponsor: Mayo Clinic○ Principal Investigator: Charles L. Loprinzi○ Protocol IDs: MC10CC, NCI-2011-00339• MC5-A Scrambler Therapy in Reducing Peripheral Neuropathy Caused by Chemotherapy<ul style="list-style-type: none">○ NCT ID: NCT01290224○ Sponsor: Mayo Clinic○ Principal Investigator: Charles L. Loprinzi○ Protocol IDs: MC10C8, NCI-2011-00109, 10-007874○ NOT ENROLLING AT PRESENT [CLINICALTRIALS.GOV; ACCESSED 7.16.12]• MC-5A for Chemotherapy Induced Peripheral Neuropathy<ul style="list-style-type: none">○ NCT ID: NCT01261780○ Sponsor: University of Wisconsin, Madison○ Principal Investigator: Toby Campbell○ Protocol IDs: OS10328• Electrical Stimulation Pain Therapy in Treating Chronic Pain and Numbness Caused By Chemotherapy in Patients With Cancer<ul style="list-style-type: none">○ NCT ID: NCT01196442○ Sponsor: Virginia Commonwealth University, Massey Cancer Center○ Principal Investigator: Thomas J. Smith○ Protocol IDs: MCC-13098, NCI-2010-01945• Treatment of Chronic Neuropathic Pain Caused by Chemotherapy<ul style="list-style-type: none">○ Competitive Technologies, Inc. |
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Utilization Management Policy

Appendix 1

Risk of Bias (limitations in study design or implementation)

Title: Marineo G, Iorno V, Gandini C, et al. Scrambler therapy may relieve chronic neuropathic pain more effectively than guideline-based drug management: results of a pilot, randomized, controlled trial. *Journal of Pain and Symptom Management* 2012; 43:87-95

| Domain | No. | Source | Assessment | Notes |
|--------------------|-----|--|-------------|--|
| A | 1 | Was the method of randomization adequate? | No | Assigned in consecutive order |
| B | 2 | Was the treatment allocation concealed? | No | Study explicit that allocation was not concealed |
| C | | Was knowledge of the allocated interventions adequately prevented during the study? | | |
| | 3 | Was the patient blinded to the intervention? | No | |
| | 4 | Was the care provider blinded to the intervention? | No | |
| | 5 | Was the outcome assessor blinded to the intervention? | No | |
| D | | Were incomplete outcome data adequately addressed? | | |
| | 6 | Was the drop-out rate described and acceptable? | Yes | No drop-outs or loss to follow-up (author communication) |
| | 7 | Were all randomized participants analyzed in the group to which they were allocated? | Yes | |
| E | 8 | Are reports of the study free of suggestion of selective outcome reporting? | Yes | |
| F | | Other sources of potential bias: | | |
| | 9 | Were the groups similar at baseline regarding the most important prognostic indicators? | Yes | Table 2 |
| | 10 | Were co-interventions avoided or similar? | Yes | |
| | 11 | Was the compliance acceptable in all groups? | Yes | Author communication |
| | 12 | Was the timing of the outcome assessment similar in all groups? | Yes | |
| Total Score | | | 6/12 | Low Risk of Bias |

Interpretation:

- Low risk of bias = when at least 6 of the 12 criteria have been met and the study has no serious flaws (e.g., 80% drop-out rate in 1 group).
- High risk of bias = Studies with serious flaws, or those in which fewer than 6 of the criteria are met

Reference: Furlan AD, Pennick V, Bombardier C, van Tulder M. 2009 Updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* 2009; 34:1929-1941

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Appendix 2

Risk of Bias (limitations in study design or implementation)

Title: Sabato AF, Marineo G, Gatti A. Scrambler therapy. *Minerva Anestesiologica* 2005; 71:479–482

| | | |
|--|---------|--|
| Clear study objective/question | Yes | |
| Well-defined study protocol | Yes | |
| Explicit inclusion and exclusion criteria for study participants | No* | Methods used to diagnose neuropathic pain, sciatic pain, and failed back surgery syndrome were not described |
| Specified time interval for patient recruitment | No* | |
| Consecutive patient enrollment | Unsure* | |
| Clinically relevant outcomes | No | Pain intensity, a patient-important outcome, was measured only for response immediately following treatment. The durability of outcomes was not assessed. Impact on disability and HRQoL were not assessed |
| Prospective outcome data collection | Yes | |
| High follow-up rate | Yes | Immediate post-treatment assessment |

* = High risk of selection bias; HRQoL = Health-related quality of life

Source: Chan K, Bhandari M. Three-minute critical appraisal of a case series article. *Indian Journal of Orthopaedics* 2011; 45:103–104



Utilization Management Policy

Policy History/Revision Information

| Date | Action/Description |
|------------|---|
| 10/18/2012 | Original effective date |
| 4/18/2013 | Annual review and approval |
| 4/17/2014 | Annual review and approval; Policy rebranded "Optum* by OptumHealth Care Solutions, Inc." |
| 4/16/2015 | Annual review and approval |
| 4/21/2016 | Annual review and approval completed |
| 4/20/2017 | Annual review and approval completed; Legal entity name changed from "OptumHealth Care Solutions, Inc." to "OptumHealth Care Solutions, LLC." |
| 4/26/2018 | Annual review and approval completed |
| 4/25/2019 | Annual review and approval completed |
| 4/23/2020 | Annual review and approval completed |

Contact Information

Please forward any commentary or feedback on Optum utilization management policies to: policy.inquiry@optumhealth.com with the word "Policy" in the subject line.

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PLAIN LANGUAGE SUMMARY

Calmare[®] ***Pain Therapy Treatment***

Utilization Management Policy # 485

Plain Language Summaries are a service provided by *Optum*^{*} by *OptumHealth Care Solutions, LLC* to help patients better understand the complicated and often mystifying language of modern healthcare.

Plain Language Summaries are presented to supplement the associated clinical policy or guideline. These summaries are not a substitute for advice from your own healthcare provider.

What is Calmare therapy and what is known about it so far?

Calmare (also known as Scrambler) therapy is a non-invasive pain therapy device for the management of severe chronic and acute pain. It is used when more common treatments such as medication are ineffective. Patients are connected to the Calmare Pain Therapy Treatment device by small electrodes (similar to those used in EKG and other medical procedures) that are placed on the skin near the area where there is pain. The device sends a very low current of electrical stimulation through the nerve fibers attempting to block pain signals to the brain.

The uses of this therapy for nerve pain caused by disorders that are not due to cancer (noncancer-related) such as sciatica, low back pain, post-surgical pain, etc. are largely based on very low quality clinical research. There is a need for higher quality information in order to make confident judgments about benefits and risks.

How was Calmare therapy evaluated?

A work group of clinicians was assigned to review the available research. The internet was searched for articles about Calmare (Scrambler) therapy. The work group independently examined the selected research studies. A broadly accepted rating scale was used. Possible ratings were high, moderate, low, or very low quality. Additionally, the positions and guidelines of other professional and healthcare groups were evaluated.

Before it was approved, the policy was presented to a series of committees that included independent health care practitioners.

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What did the work group find?

There is only limited research about the effectiveness of Calmare therapy for the treatment of nerve pain due to noncancer-related disorders. The overall research quality was rated as *low*. Better quality studies are needed.

It was not possible to make a determination that Calmare therapy provided more benefit, when compared to generally recommended treatments for pain management.

What were the limitations of the information?

Each of the studies involved several small groups of people. It is uncertain that the results apply to most people with similar disorders.

The use of Calmare therapy for many for the treatment of nerve pain due to noncancer-related disorders such as neck pain has not been studied.

What are the conclusions?

Calmare (Scrambler) therapy is viewed as *unproven and not medically necessary* for the treatment of noncancer-related nerve pain. Further research is needed before its use can be considered an established treatment option for any spinal condition.