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Predictive Factors Associated with Success and Failure for Calmare (Scrambler) Therapy: A Multi-Center Analysis

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Abstract

Objective: Calmare (Scrambler) therapy is a novel therapeutic modality that purports to provide pain relief by "scrambling" afferent pain signals and replacing them with "non-pain" information via conventional lines of neural transmission. The goal of this study is to identify which factors are associated with treatment outcome for Calmare therapy.

Methods: Data were garnered from 3 medical centers on 147 patients with various pain conditions who underwent a minimum of either 3 Calmare therapies on consecutive days or 5 therapies overall. A successful outcome was pre-defined as $\geq$ 50% pain relief on a 0-10 numerical rating scale that persisted for longer than 1-month after the last treatment. Variables evaluated for their association with outcome included age, gender, study site, baseline pain score, etiology, type of pain, diagnosis, treatment compliance, co-existing psychopathology, opioid use, antidepressant use, and membrane stabilizer use.

Results: Overall, the success rate was 38.1%. Variables found to be associated with a positive outcome in multivariate logistic regression included the presence of neuropathic (OR 24.78, 95% CI 2.47 – 248.97; p=0.006) or mixed (OR 10.52, 95% CI 1.09 – 101.28; p=0.042) pain, and treatment at either Walter Reed (OR 6.87, 95% CI 1.60 – 29.51; p=0.010) or Seoul National University (OR 12.29, 95% CI 1.73 – 87.43; p=0.012). Factors that correlated with treatment failure were disease (OR 0.04, 95% CI 0.002 – 0.59; p=0.020) or traumatic/surgical etiologies (OR 0.05, 95% CI 0.005 – 0.56; p=0.015) and antidepressant use (OR 0.47. 95% CI 0.18 – 1.02; p=0.056).

Conclusions: A neuropathic or mixed neuropathic-nociceptive pain condition was associated with a positive treatment outcome. Investigators should consider these findings when developing selection criteria in clinical trials designed to determine the efficacy of Calmare therapy.

Key Words: Calmare therapy, Chronic pain, Outcome assessment, Predictive value, Scrambler therapy

Introduction

Chronic pain is a leading cause of long-term disability. Approximately one-third of adults will suffer severe chronic pain at some point in their lives,[1, 2] and people with long-lasting pain experience a multitude of negative physical, psychological, and social sequelae.[3] The U.S. expenditures for chronic pain are estimated to exceed $600 million per year.[4]

Despite this enormous economic investment, disability rates have continued to soar, nearly doubling in the past 20 years, with chronic pain representing a leading cause across all demographics.[5] Nearly half of all cancer patients experience severe pain at the end of life.[6] In chronic non-cancer pain, pharmacological treatment with adjuvants has a modest effect in less than half of all individuals.[7] Opioid therapy has been shown to provide relief in some patients, but carries significant risks and long-term functional improvement is observed in only a minority of people.[8, 9] Interventional treatments such as injections and surgery may be useful in certain situations, but they are expensive and their ability to provide long-term benefit is questionable.[10, 11] Collectively, these sobering assessments augur strongly for the development of safer and more effective treatment modalities to address chronic pain.

Recently, Calmare (a.k.a. 'Scrambler therapy') therapy (CT) has emerged as a novel therapeutic modality for providing pain relief, with minimal side effects.[12, 13] Compared to conventional electro-analgesia, the assumed active principle underlying CT is not to inhibit pain transmission (via A-beta fiber excitation) per se, but rather to replace pain information with synthetic "non-pain" information. Although CT is often compared to transcutaneous electrical nerve stimulation (TENS) and is similar in that treatment involves the application of electrodes to the skin, it differs in several respects. First, whereas TENS positions electrode pairs on the area of pain, CT positions multiple electrode channels on normal sensory areas surrounding the area of pain (see figure 1). Second, TENS purportedly works by conveying unchanging on-off biphasic electric waves, while CT provides strings of "no pain

information" that change continuously. However, the most important difference between the two modes of therapy may be that CT produces analgesia by repetitively stimulating the surface receptors of C fibers, while TENS stimulates A-beta fibers in accordance to traditional "Gate Control Theory". In essence, patients feel a 'rippling sensation' instead of pain during treatment, with the analgesic effects ostensibly outlasting the duration of therapy. Preliminary studies on CT have reported efficacy in alleviating cancer-related pain and a host of refractory non-malignant pain conditions such as postherpetic neuralgia, postsurgical neuropathic pain, and spinal stenosis.[14-17]

Selecting appropriate candidates is critical for new treatments such as Calmare, whereby negative results may threaten to undermine the concept behind new innovations. Yet, despite numerous reports touting benefit in a wide range of pain conditions,[14-17] none have sought to identify factors associated with treatment outcome. Therefore, the objective of our study is to identify which demographic, clinical and treatment factors are associated with outcome for CT.

Participants, Materials and Methods

This multi-center study was approved by the Institutional Review Boards of Walter Reed National Military Medical Center, a large, joint service military teaching hospital; Naval Hospital -Camp Lejeune, NC, a small military treatment facility that primarily treats marines and other Department of Defense beneficiaries; and Seoul National University, a large civilian teaching institution in South Korea. All subjects treated at the military institutions were identified via prospectively maintained databases for Calmare and other complementary and alternative medical treatments. At Seoul National University, consecutive subjects treated with Calmare were identified by billing records. Inclusion criteria were age $\geq$ 18 years, chronic pain $\geq$ 3 months duration refractory to conventional treatments (e.g. non-steroidal anti-inflammatory drugs, adjuvants, nerve blocks), and a minimum of either 3 treatments on consecutive days or 5 treatments overall. The exclusion criterion was absence of 1-month follow-up data. In order to enhance power to detect differences in outcomes between variables and fortify the logistic regression model, all patients treated between January 2009 and December 2013 meeting the above-noted selection criteria were included in the analysis.

Treatment

All subjects were treated as outpatients by a physician or nurse under the supervision of a physician, who was trained in Calmare and certified by their institution, in accordance with previous published protocols.[15, 16] Between 1 and 5 sets of electrodes (i.e. channels) were used for each treatment depending on the number and size of the painful site(s). The confines of the painful areas were delineated by patient report. For each channel, one electrode was placed distal and the opposing electrode proximal to the painful area, whenever possible within the same dermatome (Fig. 1). On treatment day 1, the stimulation intensity was increased from a minimum of 10 (the lowest setting, 0.9 V) to a maximum of 70 (the highest setting, $\geq$ 4.9 V) every 5-15 minutes until the maximum strength tolerated was reached. On subsequent days, treatments were usually started at the highest tolerated

setting from the previous session and ramped-up every 5-15 minutes as tolerated. At the highest setting, the amperage range is from 3.5-5.5 mA, with the voltage varying between 6.5 and 12.5 V. Similar to previous reports, the phase duration was between 6.8 and 10.9 seconds, with the pulse rate ranging from 43-52 Hz. Each session took place in an isolated treatment room and lasted between 40 minutes and 1 hour. All subjects were advised to try to undergo treatment for at least 5, or ideally 10 consecutive days, but considering the minimal risk and cost (i.e. free at military facilities) involved in CT, we elected to treat patients who required more flexible treatment schedules.

Outcome Data and Follow-Up

Follow-up data at each institution was garnered either in person or by telephone by a disinterested research nurse not involved in treatment. A successful outcome was pre-defined as $\geq$ 50% pain relief on a 0-10 numerical rating scale (NRS) that persisted for longer than 1-month after the last treatment. In those individuals who underwent more than 1 round of treatment separated by at least 2 months between sessions, only the results of the initial round of treatments was tabulated. In addition to the binary outcome measure, the following variables were recorded for analysis: age; gender; study site, baseline and post-treatment average pain score over the past week, etiology (classified into disease, degenerative or traumatic), type of pain (neuropathic, nociceptive or mixed), diagnosis [classified into chemotherapy-induced peripheral neuropathy (CIPN), other type of neuropathic pain excluding spinal pain, spinal pain, arthralgia, groin pain or 'other'], co-existing psychopathology based on a screening evaluation and medical record review, opioid use, which was broken down into none or user [low (< 90 oral morphine equivalents / day) or high ($\geq$ 90 oral morphine equivalents / day)]; antidepressant (stratified into non-user or user), and membrane stabilizer (stratified into non-user or user). Neuropathic pain was defined as pain arising from a disease or lesion affecting the somatosensory system, and nociceptive pain was considered as pain arising from the activation of peripheral nerve endings resulting from tissue injury.[18] The classification of pain as neuropathic, nociceptive or mixed

was based on clinical evaluation, which is considered to be the current "gold standard".[19, 20] Post-treatment pain scores were recorded at the first visit at least 1 month after the last treatment session. Along with demographic and clinical characteristics, the treatment factors analyzed for any possible effect on outcome included the overall number of sessions performed, and compliance (i.e. consistency of treatment), which was classified as either poor (< 5 sessions on consecutive days), intermediate (5-9 treatments in a row or > 1-block of 4 treatments on consecutive days), or good (≥ 10 treatments on consecutive workdays). In general, most patients who received non-consecutive treatments did so for logistic reasons (i.e. they could not make 10 consecutive treatments).

Statistical Analysis

The patients were categorized into either negative or positive outcome based on the pre-defined success criterion. Patient characteristics by outcome were analysed using Student's t-test for continuous variables, and Chi-square test or Fisher's exact test as appropriate for categorical variables. A *P*-value of less than 0.05 was considered statistically significant. In subgroup analyses, the reported P-values were Bonferonni corrected to minimize the chance of a type 1 error; an adjusted $P < 0.017$ was considered statistically significant for the variables of "study site", "classification of pain", and "diagnosis".

Binary logistic regression techniques were used to quantify the relation between a successful outcome and the patient's clinical and demographic characteristics. Variables showing a trend towards statistical significance ($P < 0.2$) using univariate analysis were included in multivariate logistic regression.

Statistical analysis was performed using the SPSS Statistics program version 21.0 for windows. All parametric data are presented as the mean (SDs) and nonparametric data as numbers and proportions.

Results

Data were analysed on 147 subjects composed of 45 individuals from Walter Reed, 84 from Camp Lejeune, and 18 from Seoul National University. The demographic and clinical characteristics are shown in table 1. The mean age of the patients was 37.6 years (SD 16.9), ranging from 19 to 82. There were more male (71.4%) than female (28.6%) patients. Baseline NRS pain score was 5.8 (SD 1.9), indicating moderate pain. Slightly over half (51.0%) the subjects suffered from a painful condition secondary to trauma or surgery. A significant proportion of patients (46.9%) had a co-morbid psychiatric condition, with 31 patients (21.1%) carrying multiple diagnoses. Nearly half the patients were classified as having neuropathic pain (n = 73, 49.7%), 45 had predominantly nociceptive pain (30.6%), and 29 patients were categorized with a mixed pain condition (19.7%). Twenty-one patients (14.3%) were diagnosed with CIPN and 44 (29.9%) with another peripheral neuropathic pain disorder. Spinal pain (n = 33, 22.4%) was the most common among non-neuropathic pain diagnoses. The average number of treatment sessions was 20.3 (SD 18.4, range 3-130), with most (n = 104, 70.7%) subjects having intermediate or good treatment compliance. Nonetheless, a substantial proportion (n = 98, 66.7%) of the patients in our study received non-consecutive treatments, often over a period of weeks to months (median 26.0, IQR 51.0); however, the total number of treatments these patients received (median 15, IQR 24.0) often exceeded the recommended 10 treatments. Around 50% of all patients were on chronic opioids (n = 70, 47.6%) or membrane stabilizers (n = 77, 52.4%). Because only 7 patients were taking high-dose opioids, the low and high-dose categories were combined for analysis.

Factors Associated with Treatment Outcome in Univariate Analysis

Overall, fifty-six patients (38.1%) in the entire cohort experienced a successful outcome (see table 2). Perhaps the most prominent factor associated with treatment results was study site, with

over half of the subjects at Walter Reed (57.8%) and Seoul National (55.6%) subjects experiencing a successful outcome compared to only 23.8% at Camp Lejeune. Higher success rates were noted in older individuals (mean age of those with a successful outcome 42.5 years (SD 17.4) vs. 34.6 (SD 15.9; p= 0.007), females (54.8% vs. 31.4%; p= 0.014), subjects with neuropathic pain (50.7% vs. 22.2% for nociceptive pain; p= 0.006), CIPN (61.9% vs. 26.8% for others; p = 0.004), and those not receiving opioid treatment (46.8% vs. 28.6%; p= 0.028). No significant differences in treatment outcomes were observed based on treatment compliance or number of sessions, membrane stabilizer or antidepressant use (23.2% success rate in those on antidepressants vs. 38.5% in subjects not on antidepressant therapy; p= 0.070), etiology, baseline pain score or the presence of a concomitant psychiatric illness.

Factors Associated with Treatment Outcome in Multivariate Logistic Regression

The results of logistic regression analysis are shown in Table 3. This model accounted for 27% of the variability in the dependent variable (outcome). In the multivariate statistical model, subjects from Walter Reed (OR = 6.87; 95% CI: 1.60 – 29.51; p = 0.010) and Seoul National University (OR = 12.29; 95% CI: 1.73 – 87.43; p = 0.012) were more likely to experience a positive outcome than those from Camp Lejeune, while individuals with an etiology classified as either "disease" (OR = 0.04; 95% CI: 0.002 – 0.59; p= 0.020) or "traumatic/surgery" (OR = 0.05; 95% CI: 0.005 – 0.56; p= 0.015) were less likely than those with no known causation to obtain a successful result. In general, the type of pain significantly correlated with treatment results (P = 0.023), with neuropathic (OR: 24.78; 95% CI; 2.47 – 248.97; p=0.006) and mixed pain (OR: 10.52; 95% CI; 1.09 – 101.28; p=0.042) conditions exhibiting higher likelihoods of success than nociceptive pain states. Similar to univariate analysis, a trend was noted whereby antidepressant use was associated with a negative outcome (P = 0.056). The diagnostic categories "CIPN" and "other PNP" failed to reach attain statistical significance in multivariate regression owing to

significant co-linearity among explanatory variables.

Discussion

The main objective of this multicenter study was to identify those clinical and demographic variables associated with treatment outcome in patients undergoing CT. Overall, 38.1% of subjects experienced positive treatment results as defined by the parameters of this study. Variables found to be associated with a positive outcome multivariate logistic regression included the presence of neuropathic or mixed pain (P = 0.006 and 0.042, respectively), and treatment at either Walter Reed or Seoul National University (P = 0.010 and P = 0.012, respectively). Factors that correlated with treatment failure were disease or traumatic/surgical etiologies (P = 0.020 and 0.015, respectively) and antidepressant use (P = 0.056). Table 4 shows one proposed evaluation algorithm for CT.

Several clinical trials have reported some effectiveness with CT.[12-16] These studies have generally been performed in patients with neuropathic pain conditions such as CIPN, postherpetic neuralgia, and post-surgical neuropathic pain syndrome. Consistent with these observations, our multivariate analysis found presence of neuropathic pain was a significant predictor of a positive outcome with CT. Although Ricci et al.[16] failed to show statistically significant differences in CT responses between patients with nociceptive and neuropathic pain conditions, their study was not designed to identify outcome predictors, it contained fewer patients with each pain condition, and their method for categorizing the type of pain was not clearly reported. In our study, having a neuropathic pain condition was associated with a 25-fold higher response rate from CT than nociceptive pain; a mixed pain condition showed an 11-fold higher response rate than nociceptive pain condition. Our findings are consistent with other studies suggesting that neuromodulatory treatments work better for peripheral neuropathic than nociceptive pain.[21-24]

Recently, Smith, et al.[15] reported that CT resulted in a dramatic 59% reduction in CIPN pain beginning during the first several days of treatment. The primary endpoint of the study was to determine whether CT reduced CIPN in cancer patients by at least 20%, which was achieved in 15 of

16 patients (94%). In our univariate analysis, CT was associated a 4.4-fold increase in effectiveness for CIPN compared with other diagnoses including arthritis, spinal pain and groin pain. CIPN is well-known to be refractory to most conventional treatments, including 1st and 2nd line treatments for neuropathic pain.[25] Whereas multivariate analysis did not show that CT had any beneficial or detrimental effect on CIPN compared to other conditions, this was due in part to extensive co-linearity between CIPN and other variables that positively predicted a good outcome, and may also reflect limitations in our model. Clearly, further study is necessary in this area.

We could not detect any association between treatment compliance/ frequency and benefit, which some might interpret as suggesting that the placebo effect played a significant role in our study. Although a lack of effect (i.e. placebo response) can result in the absence of any dose-response relationship, one could also expect a higher placebo response rate in those individuals who underwent more treatment sessions.[26] Therefore, an alternative explanation is that a reduced number of sessions may be required in most individuals in order to reach the ceiling effect.

Two other findings that warrant attention are that "opioid use" was associated with a negative outcome in univariate but not multivariate analysis, and that "disease or traumatic/surgical etiology" was a negative outcome predictor in multivariate logistic regression. In terms of "opioid use," our results are consistent with multiple other studies that have shown opioid use to negatively correlate with treatment results.[27-29] Possible reasons for this association include greater disease burden in patients receiving opioid treatment, opioid-induced hyperalgesia, and a higher rate of psychopathology and secondary gain issues in this population.[30-33] It is more difficult to interpret the relationship of negative CT outcome and post-traumatic etiology in multivariate analysis, but the association may be related to the multiple mechanisms and co-morbidities (e.g. psychopathology) in this population, and the fact that few treatments have proven effective for this diverse category.[34-38] This finding is also consistent with studies that show that knowledge of abnormal MRI results may be associated with a lesser sense of well-being despite similar low back pain outcomes than not

knowing MRI results.[39]

Overall, the success rate in the study seems to be disappointingly low (38.1%), even in patients with neuropathic pain (50.7%). There are several possible explanations for our lower success rates than previously published studies.[12-16] First, our data was garnered from heterogeneous populations with sundry diagnoses. U.S. Marines from Camp Lejeune comprised a majority (57.1%) of our study sample. These service members presented with various different pain conditions (e.g. groin pain), and in the face of repeated deployments during 2 wars, were exposed to physical and psychological stressors that may not be reflective of the general population. Second, variable compliance rates may have contributed to our lower success rates. Previous clinical trials usually included patients who went through 10 consecutive sessions. Despite the finding that treatment regimen compliance did not emerge as an outcome predictor in multivariate regression analysis, only 49 patients (33.3%) completed 10 or more consecutive sessions in our study. Finally, we should consider non-standardization of treatment regimens as an explanatory factor in our disparate outcomes across treatment centers, which could have contributed to our lower than expected success rate.

There are several limitations to this study that warrant attention. The principal ones revolve around the retrospective nature of the analysis and the inherent flaws this entails, including post-hoc selection and classification of study variables, the absence of a predetermined sample size which likely precluded finding a significant effect for certain independent variables (e.g. antidepressant use), non-standardization of treatment regimens, missing data, and recall bias. We also did not include technical factors in our analysis, such as the size of the treatment area and the voltage applied, which should be explored in future research. But perhaps the main limitation specific to this study was that it included a preponderance of active duty service members who may be subject to different disease and injury patterns and who experience different psychosocial stressors, than civilian personnel. As noted above, this skewed population sample may limit the generalization of our results.

In conclusion, we found that having a neuropathic or mixed neuropathic-nociceptive pain condition, and a degenerative etiology were associated with a positive outcome in multivariate analysis. Investigators should consider these findings when developing selection criteria in future clinical trials designed to determine the efficacy of CT. Prospective studies are recommended to confirm our findings and ascertain which additional variables can be taken into account to improve the likelihood of a successful outcome for CT.

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Figure legend

Fig.1. Calmare therapy being performed a patient with neuropathic pain in his left anterior lower leg. The circles delineate the most painful areas, around which the electrodes are placed.

Tables

Table 1. Baseline demographic and clinical characteristics of study participants

Characteristic	Result
Age (mean in years, SD)	37.6 (16.9)
Gender (male / female)	105 (71.4%) / 42 (28.6%)
Study Site	
Walter Reed	45 (30.6%)
Camp Lejeune	84 (57.1%)
Seoul National University	18 (12.2%)
Etiology	
None/Unknown	20 (13.6%)
Degenerative	18 (12.2%)
Disease	34 (23.1%)
Traumatic/ Surgery	75 (51.0%)
Co-Morbid Psychiatric Condition	
None	78 (53.1%)
Mood disorder	8 (5.4%)
Anxiety disorder	9 (6.1%)

Posttraumatic stress disorder	11(7.5%)
Other[1]	10 (6.8%)
Multiple diagnoses[2]	31(21.1%)
Classification of Pain	
Neuropathic	73 (49.7%)
Nociceptive	45 (30.6%)
Mixed	29 (19.7%)
Diagnosis	
Chemotherapy-induced peripheral neuropathy	21 (14.3%)
	44 (29.9%)
Other peripheral neuropathic pain	33 (22.4%)
Spinal pain	9 (6.1%)
Arthritis/ joint pain	28 (19.0%)
Groin pain	12 (8.2%)
Other[3]	
Baseline Numerical Rating Scale Pain Score (mean, SD)	5.8 (1.9)
Number of Sessions (mean, SD)	20.3 (18.4)
Treatment Regimen Compliance[4]	
Poor	43 (29.3%)
Intermediate	55 (37.4%)
Good	49 (33.3%)
Opioid Use[5]	70 (47.6%)
No	77 (52.4%)

Low-dose	63 (42.9%)
High-dose	7 (4.8%)
Membrane Stabilizer Use	77 (52.4%)
Antidepressant Use	48 (32.7%)

Data are expressed as means (SD) or number of patients (%).

1. Other co-morbid psychiatric conditions include personality disorders, substance abuse, etc.
2. Multiple diagnoses included in both individual and "multiple" categories.
3. Other diagnoses include headaches, abdominal pain, etc.
4. Poor- < 5 sessions in a row; intermediate- 5-9 sessions in a row, or 4 sessions in a row on more than 1 occasion; Good- $\geq$ 10 sessions in a row.
5. Low-dose user- < 90 oral morphine equivalents per day; high dose user- $\geq$ 90 oral morphine equivalents per day.

Table 2. Patient Characteristics by Outcome

Characteristic	Negative Outcome (N = 91)	Positive Outcome (N = 56)	P-Value
Age (mean in years, SD)	34.6 (15.9)	42.52 (17.4)	**0.007**
Gender (N), Male / Female	72 / 19	33 / 23	**0.014**
Study Site[a]			**< 0.001**
Walter Reed	19 (42.2%)	26 (57.8%)	
Camp Lejeune	64 (76.2%)	20 (23.8%)	
Seoul National University	8 (44.4%)	10 (55.6%)	
Etiology			0.137
None/Unknown	12 (60.0%)	8 (40.0%)	
Degenerative	11 (57.9%)	8 (42.1%)	
Disease	16 (47.1%)	18 (52.9%)	
Traumatic/ Surgery	52 (70.3%)	22 (29.7%)	
Co-Morbid Psychiatric Condition			0.398
None	45 (58.4%)	32 (41.6%)	
Present	46 (65.7%)	24 (34.3%)	
Classification of Pain[b]			**0.006**
Neuropathic	36 (49.3%)	37 (50.7%)	
Nociceptive	35 (77.8%)	10 (22.2%)	
Mixed	20 (69.0%)	9 (31.0%)	
Diagnosis[c]			**0.004**
Chemotherapy-induced peripheral neuropath	8 (38.1%)	13 (61.9%)	

y	23 (52.3%)	21 (47.7%)	
Other peripheral neuropathic pain	60 (73.2%)	22 (26.8%)	
Others[1]			
Baseline Numerical Rating Scale Pain Score (mean, SD)	5.79 (1.90)	5.84 (2.01)	0.873
Number of Sessions (mean, SD)	21.22 (18.71)	18.80 (17.90)	0.436
Treatment Regimen Compliance[2]			0.775
Poor	25 (58.1%)	18 (41.9%)	
Intermediate	36 (65.5%)	19 (34.5%)	
Good	30 (61.2%)	19 (38.8%)	
Opioid Use			**0.028**
No	41 (53.2%)	36 (46.8%)	
Yes	50 (71.4%)	20 (28.6%)	
Membrane stabilizer			0.613
No	45 (64.3%)	25 (35.7%)	
Yes	46 (59.7%)	31 (40.3%)	
Antidepressant			**0.070**
No	56 (61.5%)	35 (38.5%)	
Yes	43 (76.8%)	13 (23.2%)	

Data are expressed as means (SD) or number of patients.

1. Other diagnoses included spinal pain, arthritis and joint pain, groin pain, headache, abdominal pain, etc.
2. Poor- < 5 sessions in a row; intermediate- 5-9 sessions in a row, or 4 sessions in a row on more than 1 occasion; Good- $\geq$ 10 sessions in a row.

a. In subgroup analyses of ‘study site’, statistically significant differences in outcome were found between Walter Reed and Camp Lejeune (corrected $P < 0.001$) and between Camp Lejeune and Seoul National University (corrected $P = 0.011$), but not between Walter Reed and Seoul National University (corrected $P = 1.000$). A correct $P < 0.017$ was considered to be statistically significant using Bonferroni adjustment.
b. In subgroup analyses of ‘classification of pain’, a statistically significant difference in outcome was found between the neuropathic and nociceptive pain (corrected $P = 0.003$), but no significant difference was noted between neuropathic and mixed pain (corrected $P = 0.082$) or between nociceptive and mixed pain conditions (corrected $P = 0.425$). A correct $P < 0.017$ was considered to be statistically significant using Bonferroni adjustment.
c. In subgroup analyses of ‘diagnosis’, a statistically significant difference in outcome was found only between chemotherapy induced peripheral neuropathy and others (corrected $P = 0.004$). No significant difference was noted between chemotherapy induced-peripheral neuropathy and ‘other peripheral neuropathic pain’ (corrected $P = 0.304$) or between ‘other peripheral neuropathic pain’ and ‘others’ (corrected $P = 0.029$). A correct $P < 0.017$ was considered to be statistically significant using Bonferroni adjustment.

Table 3. Factors associated with treatment outcome in multivariate analysis (Multivariate r^2 = 0.273, n = 147)

Variable	Univariable Analysis OR (95% CI)	P value	Multivariable Analysis OR (95% CI)	P value
Age	1.03 (1.01 – 1.05)	**0.007**	0.98 (0.94 – 1.02)	0.324
Female	2.64 (1.27 -5.50)	**0.01**	1.11 (0.36 – 3.42)	0.862
Study Site		**< 0.001**		**0.017**
Walter Reed	4.38 (2.02 – 9.51)	< 0.001	6.87 (1.60 – 29.51)	**0.010**
Seoul National University	4.00 (1.39 – 11.51)	0.01	12.29 (1.73 – 87.43)	**0.012**
Etiology		**0.14**		**0.022**
Degenerative	1.09 (0.30 – 3.91)	0.89	1.82 (0.37 – 9.86)	0.487
Disease	1.69 (0.55 – 5.17)	0.36	0.04 (0.002 – 0.59)	**0.020**
Traumatic/surgery	0.64 (0.23 – 1.77)	0.38	0.05 (0.005 – 0.56)	**0.015**
Co-Morbid Psychiatric Condition	0.73 (0.38 – 1.43)	0.365	-	-
Classification of Pain		**0.007**		**0.023**
Neuropathic	3.60 (1.55 – 8.33)	0.003	24.78 (2.47 – 248.97)	**0.006**
Mixed	1.58 (0.55 – 4.52)	0.399	10.52 (1.09 – 101.28)	**0.042**
Diagnosis		**0.005**		0.833
CIPN	4.43 (1.62 – 12.13)	0.004	1.34 (0.19 – 9.63)	0.771
Other PNP	2.49 (1.16 – 5.36)	0.020	1.44 (0.44 – 4.71)	0.548
Baseline Pain Score	1.01 (0.85 – 1.21)	0.870	-	-

Number of Sessions	0.99 (0.97 – 1.01)	0.440	-	-
Treatment Regimen		0.775	-	-
Compliance				
Poor	0.88 (0.38 – 2.03)	0.763		
Intermediate	0.73 (0.32 – 1.67)	0.459		
Opioid Use	0.46 (0.23 – 0.90)	**0.024**	0.55 (0.22 – 1.35)	0.192
Membrane stabilizer	1.21 (0.62 – 2.37)	0.571	-	-
Use	0.48 (0.23 – 1.03)	**0.058**	0.47 (0.18 – 1.02)	0.056
Antidepressant Use				

CIPN- chemotherapy-induced peripheral neuropathy; PNP- peripheral neuropathic pain.

Baseline reference characteristics: male; Camp Lejeune, None/Unknown etiology; no co-morbid psychiatric condition; nociceptive pain condition; 'others' for diagnosis; good treatment regimen compliance; no opioid use, no membrane stabilizer use and no antidepressant use.

Table 4. Proposed Sequential Evaluation for Calmare Therapy

Intervention	Comments
1. Confirm the pain is organic.	Non-organic conditions are unlikely to respond to treatment. Evaluation for Waddell's signs, imaging, diagnostic injections and electrodiagnosic testing are sometimes used to rule out non-organic pathology, but may be associated with false-positive and false-negative results.
2. Has patient failed conventional treatments?	Treatments proven to be effective in clinical trials should be considered first.
3. Discuss and confirm the time. commitment required for treatment.	Patients who cannot commit to the required sessions may be more likely to fail treatment.
4. Classify pain.	Patients with purely nociceptive pain may be less likely to benefit from treatment. s-LANSS and pain DETECT are 2 such instruments that can help with categorization.[19, 20]
5. Consider a trial of weaning opioids and adjuvant medications.	The concomitant use of opioids and/ or adjuvants has been shown in some studies to increase the likelihood of treatment failure.
6. Educate the patient on rehabilitation and exercise.	Immediate pain relief should be used to optimize physical therapy or exercise treatment to maximize benefit.
7. Perform interim evaluations to	If no response after 3-5 treatments, consid

assess response. er other options.

s-LANSS = Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs

Figure 1
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