Acta Biomed 2015; Vol. 86, N. 2: 149-156

Original article

Chronic pain treatment and scrambler therapy: a multicenter retrospective analysis

*Christian Compagnone, Fernanda Tagliaferri, on behalf of the Scrambler Therapy Group**
II Unit of Anesthesia, Intensive Care and Pain Therapy. University Hospital of Parma, Parma, Italy

Summary. *Background and aim:* Scrambler Therapy is a novel neuromodulation that works by electrocutaneous stimulation in a non-invasive manner through C fibers surface receptors. It substitutes pain information with synthetic "non pain" information. The primary aim of this study was to analyze the efficacy and safety of Scrambler Therapy after ten sessions related to different usage conditions and different learning curves that occur in a multi-center study. *Methods:* 201 patients have been treated with Scrambler Therapy. All the patients were suffering from chronic pain with a mean pain NRS of 7.41 (SD 2.06) before treatment. Main causes of chronic pain: post herpetic neuralgia 18.40 %, chronic low back pain (LBP) 37.31%, polyneuropathy 10.94%, and peripheral neuropathy 14.42 %. The remaining 18.93 % included chronic pain due to other causes. *Results:* The difference between pre-treatment NRS 7.41 (SD 2.06) and post-treatment 1.60 (SD 2.22) was statistically significant (P< 0.0001). The mean number of sessions per patient was 10, but 39 had complete absence of pain sooner and used fewer sessions. Only 7 patients stopped treatment due to lack of results, and 2 for personal reasons not ascribable to the treatment. Stimulation pain score of 0 during treatment, and not just pain reduction, predicts long term effectiveness, so this must be pursued by optimizing electrode positioning and correct fine-tuning of stimulation intensity. *Conclusion:* Scrambler Therapy is an efficient and safe alternative for several different types of refractory chronic neuropathic pain, with a very rare possibility of adverse events. (www.actabiomedica.it)

Key words: Scrambler therapy, chronic pain, post herpetic neuralgia, low back pain, polyneuropathy, peripheral neuropathy, persistent pain

Introduction

Chronic pain affects quality of life. People with long-lasting pain experience a multitude of negative physical, psychological and social feelings. A recent European telephone survey (EFIC) showed that chronic pain occurred in 19% of the adults contacted, seriously affecting their daily activities, social and working life. The majority had not received specialist pain treatment, and 40% felt that their pain had been poorly managed (1). A pan-European average of 40% of pain sufferers were not satisfied with the effect of the treatment they were receiving for their long lasting pain (2). Diverse alternative treatments had been proposed for this kind of patients.

Scrambler Therapy is a novel non-invasive neuromodulation technique by electrocutaneous stimulation in a non-invasive manner that works by conducting

* Scrambler Therapy Group: Francesco Amato; Giovanna Ballerini; Filippo Berlinghieri; Laura Bertini; Giorgio Bordin; Pietro Buonavolontà; Alga Cascioli; Francesca Ceccaroni; Angela Cautillo; Alma Ciaschi; Lucia Maria Dodaro; Guido Fanelli; Francesca Greco; Paola Lesignoli; Ornella Martini; Alfonso Papa; Domenico Quatrone; William Raffaeli; Mediati Rocco; Renato Velluci

impulses through C fiber surface receptors. Compared to conventional electro-analgesia, the active principle is not to inhibit pain transmission (such as TENS, implanted SCS/PNS devices), but to substitute pain information with synthetic "non pain" information. The multiprocessor apparatus is able to stimulate up to five artificial neurons placed just outside the area of pain to interfere with the pain signal transmission and replace "pain" information with artificial "non-pain" information. It is hypothesized that this therapy can "remodel" the pain system to gradually raise the subjective pain threshold with no undesirable side effects (3). The links between the active hypotheses and the observed pain relief are described on the International Patent PCT/IT2007/000647 and U.S. Patent No. 8,380,317. Overall, although nerve stimulation techniques have proven useful in a number of case series or small randomized studies, conclusive results have yet to be obtained due to the paucity of placebo-controlled trials. It is however also necessary to highlight that this specific technique differs from traditional electroanalgesia by a different active principle, theoretical reference model and neurophysiological stimulation target. Furthermore, even if no placebo controlled trials have been carried out there are some elements to keep into account. The specific ability of this therapy to systematically "zero out" pain (reduce the pain score to 0 during the treatment), the results achieved on a broad number of patients unresponsive to any other treatment, and the very large effect size compared to smaller effect sizes seen with the placebo arm in other trials treating neuropathic pain (4-8) reduce the likelihood of possible placebo effect.

The primary aim of this study has been to analyze the efficacy and security of the Scrambler Therapy after ten sessions during different usage conditions and different learning curves that occur in a multi-center study. The secondary aim has been to evaluate the outcome at 3 months.

Materials and Methods

Eight centers had participated in this retrospective observational study: Azienda Ospedaliera Universitaria di Parma (Parma), Azienda Ospedaliera Universitaria Careggi (Florence), Ospedale Sol et Salus (Rimini), Ospedale Piccole Figlie (Parma), Azienda Ospedaliera Mario Santo (Cosenza), Ospedale C.T.O Alesini (Rome), Ospedale San Vincenzo (Taormina), Azienda Ospedaliera dei Colli-Monaldi (naples). Every single treatment session was performed by a trained anesthesiologist or specialized nurse. All centers have used the MC-5A device (Scrambler Therapy® Technology) to perform the treatment.

The entire treatment consists in 10 sessions within 2 weeks, maximum 1 session a day, 45 minutes long. If pain completely resolves (zero pain) before the ten sessions, the treatment is discontinued. The treatment requires a specific protocol and usage methods learned through official training courses.

Inclusion criteria for this study were: age older than 18 years, chronic pain for at least 6 months and episodes of severe pain defined as an NRS (9,10) higher than 7 at least once a day in the last week before treatment with poor response to standard treatment. Exclusion criteria were the presence of a cardiac pacemaker or metallic prosthesis. Data has been retrieved from a unique anonymized database which has collected data from all the centers since 2012. Data include age, sex, pain scores, type of pain, duration of pain, ongoing treatment, NRS before and after the treatment session. Changes in the Brief Pain Inventory (BPI) at three months was used as the primary outcome (11).

Statistical methods

Continuous variables are described by calculating the mean and standard deviation (SD). Categorical variables are analyzed by indicating the number and percentage. The comparison between the different variables have been performed with the Wilcoxon matched-pairs signed-ranks test. A value of $p < 0.05$ is considered statistically significant. No adjustments were made for multiple comparisons.

Finally, we would like to point out that to solve problems of lack of data uniformity and operator-dependent bias, the author of Scrambler Therapy basic and applied research has developed STDM, a free dedicated software (CE certification as medical device) to be used together with the ST. In Europe the CE marking (17) indicates that this software can

increases the efficacy and safety of Scrambler Therapy, and now is therefore considered as an integral part for the correct usage of the medical device itself and its best clinical practice. In addition, STDM can support Clinical Trials in reducing operator dependent variability to a minimum. In the US FDA still does not foresee any specific certification for this type of software (Not Classified), but STDM is fully compliant to HIPAA and Safe Harbor privacy standards (18).

Results

From January to December 2012, 201 patients have been treated with Scrambler Therapy at 9 centers (table 1). The mean age was 65.53 (SD 15.4). All the patients were suffering from chronic pain with a mean NRS of 7.41 (SD 2.06) before treatment. The main causes of chronic pain included the following: post herpetic neuralgia 18.40%, chronic low back pain (LBP) 37.31%, polyneuropathy 10.94%, and peripheral neuropathy 14.42 %. The remaining 18.93 % included chronic pain due to other causes.

Pharmacological data of the patients during the treatment is shown on table 2. It is important to highlight that before treatment recruitment 55% of the patients were treated with more than one drug, and 21 % had interrupted the drug treatment due to intolerance or adverse events.

Table 1. Demographic

n=	201
Age	65.53 (SD 15.4)
Diagnoses	
PHN post-herpetic	18.40%
neuropathy	37.31%
LBP	10.94%
Polyneuropathy	14.42%
Peripheral neuropathy	18.93%
Other causes	
Pain Score at entry	7.41 (SD 2.06)

Table 2. Pain medication dose reductions

Pain killer	N= (before)	N= (after)	Eliminated
Opiates	77	55	71.42%
Anticonvulsants	62	16	74.19%
Antidepressants	20	14	70.00%
NSAID	28	3	89.28%

Figure 1 shows NRS before and after each single session. The difference between pre-treatment NRS 7.41 (SD 2.06) and post-treatment 1.60 (SD 2.22) were statistically significant (P< 0.0001). The

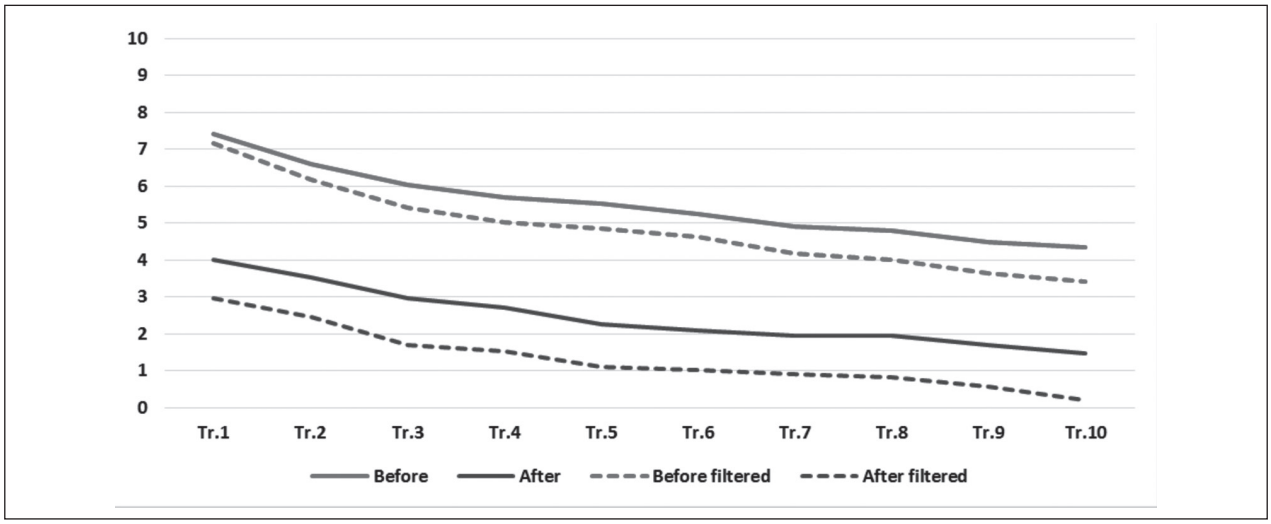

Figure 1. NRS before and after scrambler treatment session in the whole population. "Patients with Zeroed Out Pain" curves (filtered) show patients whose pain has been zeroed out during each session that make up the treatment cycle

mean number of sessions per patient was 10, but 39 had complete absence of pain before 10 sessions and were able to stop. Only 7 (3%) patients interrupted the study due to lack of results, 2 due to inability to continue personal reasons not ascribable to the treatment.

We did an exploratory analysis of those patients who had the best possible results with their pain "zeroed out", or reduced to no pain, to explore if complete pain relief was a necessary component for sustained relief. The adjusted curves represent the pain outcome during treatment sessions where the pain has been zeroed out, representing the patients who got the best result. In this case average Pain Relief increased to 96.92% (NRS reduced to 0.21). This data confirms that zeroed out pain during stimulation, and not just a pain reduction, is a primary goal that must always be pursued by optimizing electrode positioning and correct fine-tuning of stimulation intensity.

Post-herpetic neuralgia

Post-herpetic neuralgia was 18.40% of our study population. The mean NRS before treatment is 8.61 (SD 1.74). After the first session the mean NRS is 5.31. Pain after the last session is significantly lower (P< 0.0001), with a mean of 1.91 (SD 2.57). We recorded a success rate (Pain Relief >= 50%) of 86.11% .

Chronic low back pain (LBP)

Chronic low back pain was 37.31% of our study population. The mean NRS before treatment is 7.45 (SD 2). After the first session the mean NRS is 4.13 (SD 2.4). Pain after the last session is significantly reduced (p<0.0001), with a mean NRS of 1.36 (SD 1.1). We recorded a success rate (Pain Relief >= 50%) of 93.33% .

Polyneuropathy

Polyneuropathy was 10.94% of our study population. The mean NRS before treatment is 6.59 (SD 2.77). After the first session the mean NRS is 2.86 (SD 2.94). Pain after the last session is significantly reduced (P<0.0001) with a mean NRS of 1.5 (SD 1.84). Recorded (Pain Relief >= 50%) success rate of 86.36%.

Peripheral neuropathy

Peripheral neuropathy affects 14.42 % of our population. The mean NRS before treatment is 7.48 (SD 1.84). After the first session the mean NRS is 3.96 (SD 2.83). Pain after the last session is significantly reduced (P<0.0001) with a mean NRS of 2.03 (SD 2.47). Recorded (Pain Relief >= 50%) success rate of 82.75%.

Anti-epileptic therapy

In Scrambler Therapy, anticonvulsants especially in high dosage, may inhibit effectiveness due to their interference with the genesis of action potentials . In the treated group 30.84% of the patients were taking anticonvulsants for analgesic purpose. The statistic evaluation of this observation calls for a RCT with sufficiently uniform arms, also for the dosage and molecules used, and therefore is outside of this study's scope. Nonetheless, it is noteworthy to mention that the concomitant use of anticonvulsants did not reveal to have more benefit than not taking the drugs. Until large randomized trials are done, we suggest patients wean anticonvulsants as reported in a previous RCT (10).

Pain medication dose reductions

Scrambler therapy was associated with significant pain medication dose reductions, as shown in Table 2. Opiates were totally eliminated in 55 out of 77 cases (71.42%), anticonvulsants were eliminated in 46 of 62 cases (74.19%), antidepressants were eliminated in 14 of 20 (70%) cases, lastly, NSAID were eliminated in 25 of 28 (89.28%) cases.

Long-term outcome

Long term outcome was evaluated with changes in the BPI scale, as shown in Figure 2. There is a improvement in each point evaluated. The greatest modification is in the Pain, Sleep and Work items. The Pain

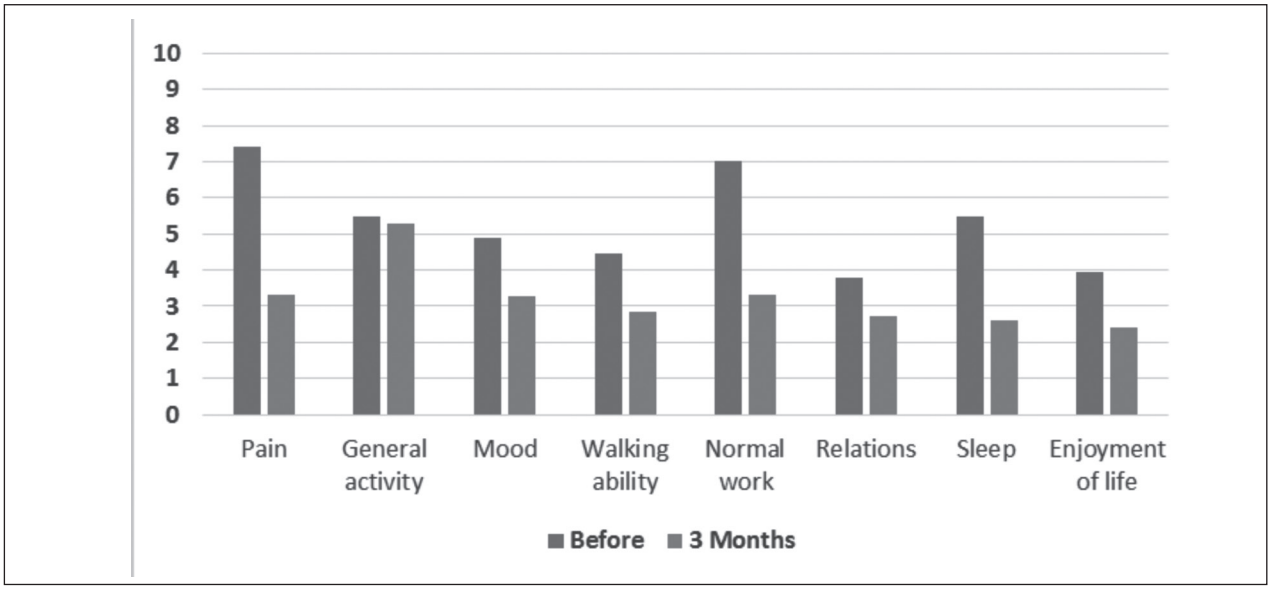

Figure 2. Changes in the BPI scale before and after 3 months of treatment

Score at entry has been reduced from 7.41 (SD 2.06) to 3.7 (SD 1.4) at three months. The quality of sleep also improved after 3 months. Sleep disorders due to pain have been significantly reduced from a mean of 5.5±3.2 to a mean of 2.6±2.7, with a 50% improvement in 53% of the patients. The influence of pain in work activities had a reduction of 52.86 %. The reduction is quantified in 4 points from 7.0±2.9 to 3.3±2.6.

Discussion

Neuropathic Chronic pain is common and often difficult to treat. Different diseases could lead to neuropathic pain including postsurgical pain, post-herpetic neuralgia (PHN), spinal cord stenosis (SCS), Complex Regional Pain Syndrome (CRPS), Diabetic peripheral neuropathy (DPN), and chemotherapy induced peripheral neuropathy. Unfortunately, conventional treatments such as opioids, neuroleptics, and other drugs have a high rate of failure and a high incidence of side effects. Chronic pain of moderate to severe intensity occurs in 19% of adult Europeans, seriously affecting the quality of life and nearly half received inadequate pain management (2). A few proposals to reduce chronic pain include the use of electrical nerve stimulation, e.g., neuromodulation with electrical stimulus (spinal cord stimulation and subcutaneous peripheral nerve stimulation) and transcutaneous electrical nerve stimulation (TENS). Spinal cord stimulation can give pain relief but involves invasive expensive technology with the possibility of serious adverse effects. TENS and Scrambler Therapy (ST) have only one point in common: the non-invasive electrical stimulation. They are technically different and have a different mechanism of action. TENS or implanted stimulators, are based on the Gate Control theory and for this reason are specifically designed to stimulate myelinized fibers and avoid the stimulation of C fibers, in line with conventional electro-analgesia general standards. In contrast, Scrambler Therapy specifically uses C fibers to relieve pain. (2 international patents, US patent). Various hypotheses have been developed to explain the mechanisms of action of the clinical benefit obtained from electrical nerve stimulation, e.g., supraspinal processes, modulation of descending inhibitor pathways, peripheral release of calcitonin, increase in gate control for pain threshold, reduction in windup phenomenon, and reduction in impulses from damaged nerves.

Only a few studies had tested the efficacy of ST. Four of them have potential biases because they were done by the author of Scrambler Therapy basic and

applied research, and owner of patents on technology application. However all the clinical trials signed by the author have been carried out independently in accredited University or public hospital facilities without any economic sponsorships of the trial.

In 2003, the first study was performed on a small group of 11 patients with pancreatic cancer; all were considered responders (reduction in pain intensity and gradual increase of the duration of analgesia and pain threshold), and nine were able to suspend previous drug treatment (3). A second study was made on 226 patients suffering from severe refracted neuropathic pain and reported 80% of responders (pain relief >50%), 10% of partial responders (pain relief from 25% to 49%), and 10% of non-responders (12). A third study was a randomized trial between ST against conventional pharmacologic treatment in 56 patients. The principal pathology was post surgical neuropathic pain 28 (50% of cases). After three months from the ST, patients had a reduction of 6 points in NRS and only 2 points in conventional treatment arms (13). The fourth study (14) was done on 10 patients with PHN. The average pain score rapidly diminished from 7.64 ± 1.46 at baseline to 0.42 ± 0.89 at 1 month, a 95% reduction, with continued relief at 2 and 3 months. Patients achieved maximum pain relief with less than 5 treatments.

In one independent published study (15), 73 patients with cancer and non-cancer derivate pain were included. A significant reduction after 10 sessions was obtained. However, one month outcome demonstrated the reduction of only 3 points from the basal NRS (very different from other results). However, this independent study seems not to have fully complied to ST guidelines and standard protocols (16), and shows some bias for this reason. Alternatively, it may represent achievable results early in the learning curve.

Our study is the first ST multi-center independent work published. It involves 9 different centers, including different common observed causes of chronic neuropathic pain. The intention of the authors is to reflect the real current clinical medical practice of this therapy. We observed a statistical and clinical significant reduction in the NRS scale after the first session that is maintained after the 10 sessions of the protocol. Mononeuropathy and Polyneuropathy have respectively the lower and the higher rate of failure. One probable cause of this difference could be the difficulty in positioning the electrodes in the multidistrict distribution of the polyneuropathy. In line with the previously published studies, no adverse event have been observed in our populations.

Implied Bias in Scrambler Therapy clinical studies

Scrambler Therapy is a partly operator dependent methodology. Treatment success is highly dependent on the ability of the operator to zero out pain during each single treatment without patient having discomfort. Failure to zero out pain during each treatment session leads to unsatisfactory results and is also the variable that could determine the highest study bias, creating the possibility of false non responsive patients. According to the researcher who developed the therapy, zeroing out pain during stimulation in normal usage conditions is always possible. Therefore a truly non responsive patient is someone who despite having experienced zero pain at each treatment session shows no relevant benefit during the treatment cycle and at the end of the treatment. Actual experience has confirmed that in fact more expert operators can zero out pain during the treatment where less experienced ones have failed, although this has not been formally studied.

In fact, data coming from different publications are rather heterogeneous. Documented success rates that exceed 90% assume best usage ability. This trial reproduces the heterogeneity of the previous ones in line with different usage ability and learning curves.

The table 3 illustrates the different results achieved in the centers involved in the study. Note that notwithstanding the significant difference between the highest and lowest performance scores (50-97.7%), the success rate at the end of the cycle is always very high, and results are consistent with the previous publications even considering the heterogeneity of the operators.

The study seems to confirm strong operator dependent variable recorded in the previous clinical trial outcomes. Our experience shows that before starting a clinical trial an operator, apart from proper training and full protocol compliance, must have completed an adequate learning curve through the preliminary treat-

Table 3. Degree of pain relief achieved at each center

Pain Center	NRS Before	NRS end cycle	N	Pain Relief >=50%
1	7,06	1,63	65	87.69%
2	9,4	2,8	5	80.0%
3	7,65	2,24	29	72.41%
4	7,77	0,77	45	97.77%
5	6,63	2,09	11	81.81%
6	7,5	1,75	4	75.00%
7	7,5	3,4	10	50.0%
8	6,15	0,53	13	92.30%
9	8,15	1,68	19	84.21%

ment of a broad range of patients. This turns out to be the key condition for uniformity and higher success rates among different clinical trials.

Long-term Outcome: The reduction of the Pain component in BPI is lower than in the previous trials. There could be multiple explanations. Multiple operators can influence the outcome because ST appears to have a high operator variability because it involves placement, movement, and adjustments of the therapy. Patients may have different response rates to electrical stimulation just like with pharmacologic placements. There may be a learning curve that requires a certain number of cases, such as with cardiac surgery, and there may be a volume-quality relationship like with many complex procedures. The placebo effect of spending an hour with an operator may vary from person to person. However, we obtained not only an early improvement in pain sensation (after the very first treatment) but also a persistent clinically and statistically important reduction of pain and how pain interferes with life. The quality of life has improved in a high percentage of patients.

Conclusion

ST is an efficient and safe alternative for several different types of refractory chronic neuropathic pain, with a very rare possibility of adverse events. A high percentage of patients suffering neuropathic pain obtained a sustained relief in different clinical settings. It is important to highlight that for the nature of this research, this data represent in the opinion of the authors, a trustworthy snapshot of the ST results in the current clinical experience.

References

1. http://www.ausl.fe.it/cure-palliative/aree-tematiche/attivita-di-ricerca/macondo-sintesi-dei-risulati-per-il-livello-regionale.
2. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. European Journal of Pain 2006; 10: 287-333.
3. Marineo G. Untreatable pain resulting from abdominal cancer: new hope from biophysics? JOP 2003; 4 (1): 1-10.
4. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2012 Dec 12; 12: CD008242. doi: 10.1002/14651858.CD008242.pub2. Review.
5. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2014 Apr 27; 4: CD007938. doi: 10.1002/14651858.CD007938.pub3.
6. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane Review. Spine (Phila Pa 1976). 2014 Apr 1; 39 (7): 556-63. doi: 10.1097/BRS.0000000000000249.
7. Botteman M. Systematic review and meta-analysis of pharmacological therapies for pain associated with postherpetic neuralgia and less common neuropathic conditions. Int J Clin Pract 2014; 68 (7): 900-18.
8. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. Cochrane Database Syst Rev 2013 Aug 29; 8: CD006146. doi: 10.1002/14651858.CD006146.pub2. Review.
9. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL: Defining the clinically important difference in pain outcome measures. Pain 2000; 88: 287-94.
10. Farrar JT, Young JP Jr., LaMoreaux L, Werth JL, Poole RM: Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001; 94: 149-58.
11. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 2004; 5 (2): 133-7.
12. Sabato AF, Marineo G, Gatti A. Calmare therapy. Minerva Anestesiol 2005; 71 (7-8): 479-82.
13. Marineo G, Iorno V, Gandini C, Moschini V, Smith TJ. Scrambler therapy may relieve chronic neuropathic pain more effectively than guideline-based drug management: results of a pilot, randomized, controlled trial. J Pain Symptom Manage 2012; 43 (1): 87-95.
14. Smith TJ, Marineo G. Treatment of Postherpetic Pain With Scrambler Therapy, a Patient-Specific Neurocutane-

ous Electrical Stimulation Device. Am J Hosp Palliat Care 2013 Jul 8. [Epub ahead of print]
15. Ricci M, Pirotti S, Scarpi E, Burgio M, Maltoni M, Sansoni E, Amadori D.Managing chronic pain: results from an open-label study using MC5-A Calmare® device. Support Care Cancer 2012; 20 (2): 405-12.
16. Marineo G. Inaccuracy in the article "Managing chronic pain: results from an open-label study using MC5-A Calmare device in Support Care Cancer". Support Care Cancer 2011; 19 (10): 1483-4.
[17. Fouretier A, Bertram D. New regulations on medical devices in Europe: what to expect? Expert Rev Med Devices 2014; 11 (4):351-9.
18. http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/De-identification/guidance.html. Accessed September 15, 2014

Received: 15 March 2015
Accepetd: 18 March 2015
Correspondance:
Christian Compagnone, MD
II Unit of Anesthesia, Intensive Care and Pain Therapy
University Hospital of Parma, Parma, Italy
Tel. +39 0521-703567
Fax +39 0521-702863
E-mail: ccompagnone@parmanesthesia.com