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Inside the Scrambler Therapy, a Noninvasive Treatment of Chronic Neuropathic and Cancer Pain: From the Gate Control Theory to the Active Principle of Information

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Abstract

Scrambler therapy (ST) is an electro-analgesia therapy for the noninvasive treatment of chronic neuropathic and cancer pain based on a new generation of medical device that uses 5 artificial neurons and is based on a novel theoretical model the differs from gate control theory. The active principle with Scrambler Therapy is such that synthetic "non-pain" information is transmitted by C fiber surface receptors. This is a different theoretical mechanism than the traditional electric stimulation of A-Beta fibers to produce paresthesia and/or block the conduction of nerve fibers to produce an analgesic effect, that is, via TENS (transcutaneous electrical nerve stimulation) machines. Scrambler therapy was developed to treat chronic neuropathic pain and cancer pain resistant to opioids and other types of treatments. The goal of Scrambler Therapy is to eliminate pain during treatment and allow for long-lasting analgesia after a series of 10 to 12 consecutive treatments performed over a 2-week period. The aim of this review is to clarify the underlying theory of Scrambler Therapy and describe the appropriate usage method that maximizes its effectiveness while reducing bias and deepen the explanation of the artificial neuron technology associated with Scrambler Therapy.

Keywords

artificial neurons, cancer pain, chronic pain, drug resistance, electro analgesia, gate control theory, neuropathic pain, opioids, Scrambler Therapy

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Introduction

Scrambler therapy is aimed at creating a non-invasive highly effective treatment for chronic neuropathic and cancer pain, which is resistant to other treatments. A long-standing and commonly accepted model used to understand mechanisms of pain transmission and perception has been the gate control theory.[1] Despite the time elapsed since its introduction in 1965, this theory still remains relevant today. However, it has been revised and updated and some aspects of the theory have been redefined.[2,3]

Since chronic neuropathic pain is characterized by abnormal function of the somatosensory nervous system, the gate control theory does not easily lend itself to the development of a new type of therapy.

On the other hand, in acute pain, where the cause/effect relationship between nociceptive stimulus and lasting pain follows the normal physiological response, the gate control theory is consistent and is confirmed by experiments.

It is interesting to note that the gate control theory is apparently in complete contrast with the Scrambler Therapy model, since C fibers and not A-Beta fibers are stimulated. Therefore, if we consider only the differential effect of the electrical activities between these 2 branches as required by the gate control theory, the stimulation of the C fibers must produce pain. In fact, if you eliminate the non-pain information from the emissions of Scrambler Therapy making it

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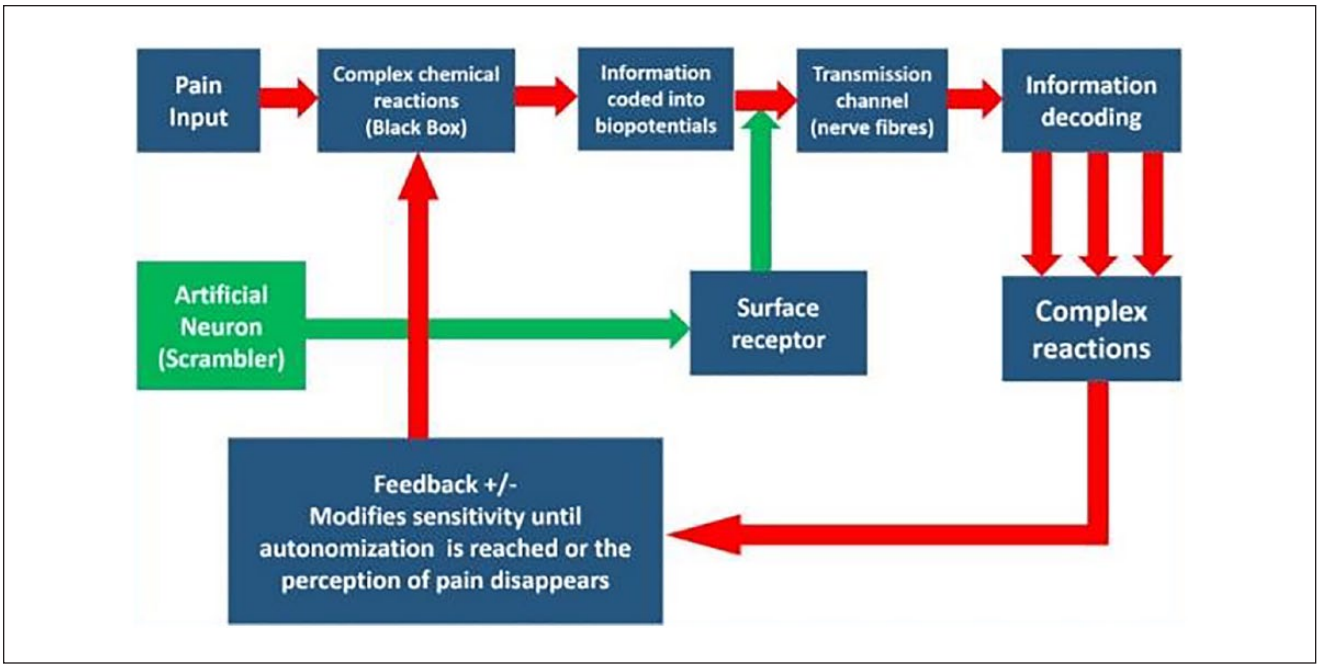

Figure 1. Simplified model of Scrambler Therapy.

similar to a TENS (transcutaneous electrical nerve stimulation), this is exactly what happens. For this same reason, Scrambler Therapy requires careful positioning of the electrodes, always guided by patient feedback, so as to use only nerve pathways that do not present structural or functional alterations capable of degrading or not correctly conveying the synthetic information of "non-pain." The result of the loss of information due to the impossibility of transmitting it correctly always transforms Scrambler Therapy emissions into simple electrical stimulus, which in addition to being ineffective, can easily produce pain instead of analgesia.

In a nutshell, the gate control theory addresses the activity of the nervous system in terms of "quantitative" electric impulses. However, the qualitative element is that these electric impulses are the basic information code by which the nervous system can be interpreted in a cybernetic model. In this broader context, pain can be interpreted analytically in terms of pure information[4] and chronic pain as a plastic modification of the pain system governed by information.[5] This is illustrated in Figure 1.

Consequently, the therapeutic approach is no longer to inhibit the transmission of pain, but to transform the information of pain into "non-pain" using the same pathways. In the Scrambler Therapy model, information becomes the central point of control of the plasticity of the pain system, both in the genesis of chronicity (induced by endogenous information of pain repeated over time) and in its regression (induced by synthetic information of "no pain" repeated over time). The theoretical expectation is therefore that of an immediate and complete analgesic effect in treatment, and of a return to normal physiological response after one or more cycles of treatment.

As far as the concept of information is concerned, there are different ways to represent it in a formally correct analytical way, but the most used model in the scientific and technological field is that of the Shannon information theory, which for this reason has also been used in Scrambler Therapy.

To put it simply, the fundamental elements of information theory are represented by an information source, a transmitter, a transmission channel, a receiver, a user, and a source of disturbance that acts on the transmission channel. This scheme, shown in Figure 2, can be applied to all forms of technological or biological transmission, identifying their functional counterparts.

Information theory, in addition to providing a general reference scheme for the coding and remote transmission of information, allows its mathematical treatment. Shannon succeeded in defining the equation with which to calculate the level of unpredictability of an information source, very similar to that with which Boltzmann had calculated the entropy of a thermodynamic system. For this reason, John Von Neumann (one of the pioneers of the computer) suggested adoption of the term *entropy* to indicate the complexity of the information available at the source in any communication system.

In practice, a reduction in entropy reduces the complexity of the signal, hence the number of bits (binary system used in computers) needed to encode it, and its degree of

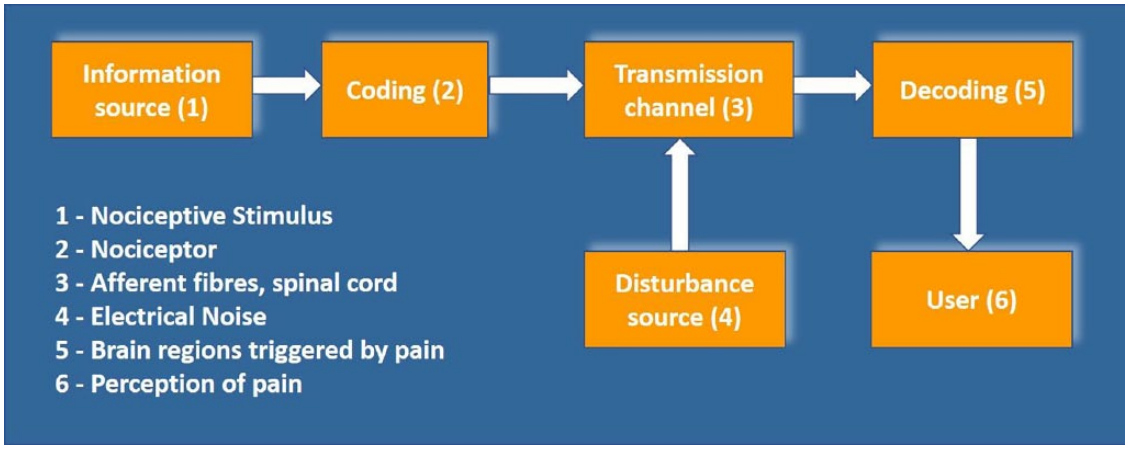

Figure 2. Information theory diagram.

uncertainty toward the receiver. In other words, if random characters are typed to produce random sequences, the possible strings (messages) are near endless. If, on the other hand, the typing is "constrained" to produce only a limited number of words of the English language, the number of possible messages is drastically reduced. A similar problem exists in the Scrambler Therapy where the only messages that one wants to transmit are those that can be interpreted by the central nervous system as "non-pain." It is therefore necessary to structure and optimize the synthetic information for the minimum entropy compatible with this purpose, which also means reducing the uncertainty in the interpretation of the message.

Artificial Neurons Technology

The Scrambler Therapy machine is based on 5 artificial neurons controlled by an optimized algorithm to provide safety and effectiveness. A neuron typically receives, processes, and transmits information. Artificial neurons from Scrambler Therapy perform the same functions through the hardware and software synergy specifically designed for this purpose. The hardware receives information from the algorithm that creates the strings of "non-pain," and processes them by transforming them into flows of synthetic action potentials (i.e. created by technology) functionally compatible with endogenous ones. The resulting emission is calibrated to synchronize the surface receptors of the C fibers, which once engaged will continue to propagate the information generated by artificial neurons endogenously.

Preliminary clinical trials to verify efficacy and safety were conducted at the University of Rome Tor Vergata from 1999 to 2006 and involved 2297 cases of various types of serious neuropathic pain that was resistant to medications and/or electro-analgesia. These data were formalized and presented in Italy in 2006 during the fourth and fifth National High Specialization course on neuropathic pain.

The success rate, defined as pain relief of more than 50% was reached in 80% of cases at approximately the 2-month follow-up visit. No substantial side effects have been observed.

Scrambler Therapy Device

Scrambler therapy has unique characteristics dependent on specialized software and a hardware module OEM (original equipment manufacturer) developed for this purpose. Therefore, the manufacturer that uses the OEM module to build the medical device, cannot independently change the clinical features of the device and change the core technology of the artificial neurons. Such change would require new clinical trials to be contacted to redetermine the effectiveness and safety characteristics.

The Scrambler Therapy device currently available (Figure 3) using this OEM technology can transmit information recognizable as "self" and "non-pain" to the central nervous system (CNS) in line with the original specifications that have been used in the clinical trials before it was marketed. "Self" and "non-pain" information sequences generated by the Scrambler Therapy artificial neurons are signals that are capable of producing various sensations that replace pain signals transmitted via C-fiber surface receptors.

The electrical stimulus is specifically designed to excite C fibers by using pulses with an appropriate width.[6]

Other properties of form/function/modulation allow the encoding of information strings to be able to substitute pain information with synthetic "non-pain" information.

Figure 3. Scrambler therapy technology device MC-5A. FDA 510(k) Clearance: # K142666, CE certified: #CE 0476.

This was done by digitally synthesizing 16 different main kinds of action potentials with variable geometry, very similar to the endogenous kind, which produce different perception effects depending on the string-sequence in which they are assembled over time and how they are modulated. An algorithm dynamically generates the specific strings (messages) of "non-pain" information, in order to try to achieve the goal of immediate and complete analgesia, causing a remodulation of the pain system with a high level of safety and long-term efficacy.

Perception of "non-pain" information and use of clinical trials

Sensory deceptions produced by "painless" information are very well tolerated, and in some case manifest themselves also as pleasant sensations similar to a massage, likely attributable to the stimulation of tactile C fibers. Patients rarely perceive some strings of information as "itching," certainly less pleasant, but still effective for analgesic purposes. More frequently, during the adjustment of the intensity of stimulation patients may experience feelings of "burning. Normally this is a sensory deception that fades with the increase of the intensity of stimulation, a parameter that determines the correct transmission of information in its integrity. If the adjustment of the stimulation level is not sufficient to eliminate burning, the electrodes must be moved because the information is not transmitted correctly by the available receptors. Other times, the patient can report a generic "discomfort" difficult to describe exactly. In general, this happens in patients with severe neurological lesions and/or subjected to the action of analgesic drugs that can confuse the perception of pain by incorrectly guiding the operator to the positioning of the electrodes. In this case too, it is usually sufficient to move the electrodes away from the area of pain until the desired effect is achieved. These abnormal sensations are particularly important because they indicate to the operator an incorrect positioning of the electrodes or an incorrect level of stimulation, allowing him or her to correct these errors.

It is also important to remember that to obtain the full and immediate analgesic effect of the Scrambler Therapy, it is sufficient for the patient to feel appropriate stimulation under the electrodes, provided that the entire positioning and adjustment procedure is performed correctly.

Efficacy and Safety Issues

To determine and understand efficacy and safety issues, one needs to consider that, with only 16 different synthetic action potentials adequately modulated and assembled in information strings, in theory, one can build millions of different sequences that interact with C-fiber surface receptors, which may determine different possible physiological responses. The creation and selection of this information is designed to be able to result in the immediate control of pain along with long-term pain relief and treatment safety. More specifically, the remodulation of the pain system is a dynamic process that requires significant variability of the strings of "non-pain" information; this dynamic information needs to be effective in an environment which is characterized by neurological damage and various pain characteristics.

The remodulation of the pain system means the suppression of chronic pain and return to a normal physiological response with regression of unpleasant symptoms, such as shooting or burning pain, allodynia, hyperalgesia or altered sensation.

In this context, extensive preliminary work has been necessary to verify the selection of strings of information that are effective and safe in a variety of pain syndromes. The algorithm that assembles information strings is essentially based on probabilistic criteria rules, which are not modifiable by the operator. These criteria determine dynamic properties of form-function strings of generated impulses (ie, information coding). An information string is made up of a series of impulse packets created from the digital synthesis of action potentials. Each new packet is created, accounting for previous outputs; these dynamically modify the probability selection of main variables that determine, in real-time, the characteristics of the new packet. Briefly, we use an algorithm based on dynamic probabilistic criteria, by which we mean a system capable of progressively modifying its choices based on analytical rules that determine new output possibilities in controlled variables. The drastic reduction of randomness deriving from this algorithm implicitly and meaningfully reduces information entropy. Except for the level of stimulation, which the operator can vary, all parameters of the treatment are fully automated.

In this final form, the many possible information sequences created by the 16 synthetic action potentials, adequately modulated and assembled in dynamic strings, have intentionally been limited to 256.

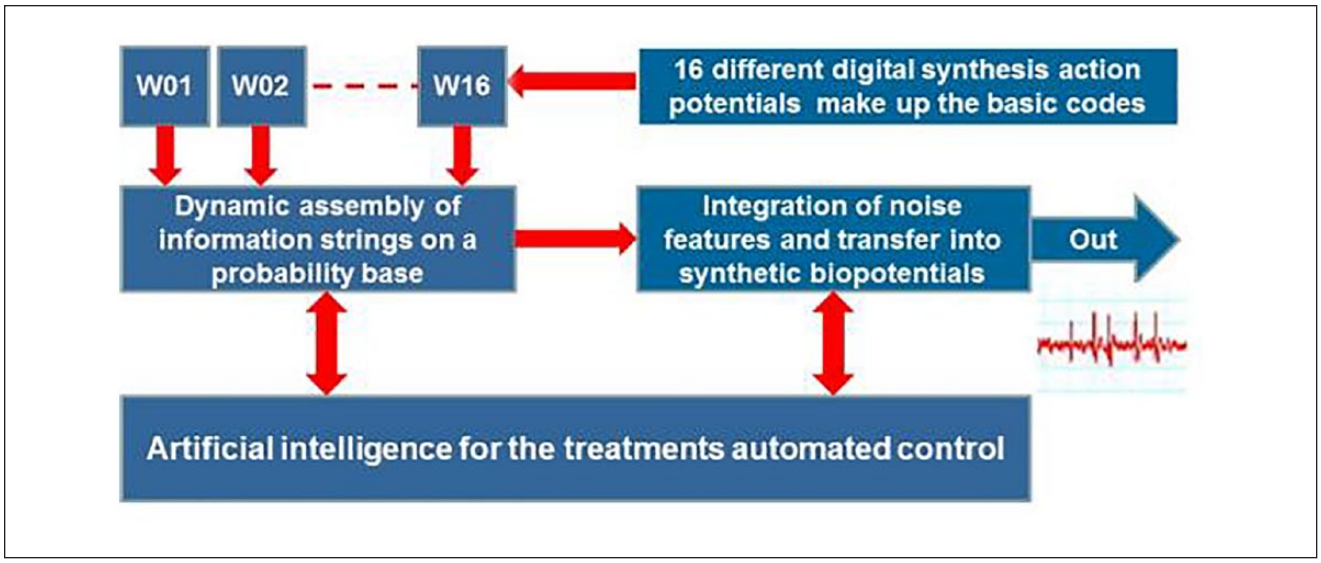

Figure 4. Block diagram of an artificial neuron. The blocks from W01 to W16 representing the 16 different synthetic action potentials used to create with appropriate dynamic assembly and modulations 256 information strings (messages) of "no pain" used in the treatment. In biological systems, according to the information theory scheme there is usually also "noise," which is simulated and integrated into the main information to make the emission of the Scrambler Therapy as "self" more recognizable.

To better understand what this means in practical terms, the 16 synthetic action potentials can be considered as 16 different letters of the alphabet. For dynamic strings one can think of a series of messages composed of various associations of different letters. In this way, the information content changes dynamically over time. Since millions of different messages can be built with 16 letters, and many of these messages will not meet the necessary criteria of effectiveness and security, the algorithm limits their creation to only 256. In conclusion, the 256 dynamic strings generated by Scrambler Therapy are nothing more than the 256 different types of "painless" information used to produce the desired analgesic effect (Figure 4). In so doing, it was possible to verify with great accuracy its efficacy and safety before testing it on a broad range of cases with different types of neuropathic and cancer pain. In view of these issues, it is quite clear that the concept of similarity that only considers the parameters of frequency, pulse width and intensity (used in other devices) is not applicable because they do not generate and do not characterize the information of "no pain". In this sense any modification of the emissions of the Scrambler Therapy in the form and organization of the flows in time, is functionally equivalent to the modification of the chemical formula of a drug.

About the FDA 510(k) Clearance

For marketing authorization in Europe, Scrambler Therapy followed the normal new medical device procedure that calls for the production of specific clinical trials to demonstrate the efficacy and safety of the new device in its clinical use in a broad range of cases. In the United States, the FDA (Food and Drug Administration) has various ways for the approval and clearance of medical devices. An option is to choose a short procedure, also known as 510(k) "Substantial Equivalence". This procedure calls for indication of one or more medical device of the same reference category (in this case, electro-analgesia). However, during the 510(k) authorization process, the FDA realized the complete difference of Scrambler Therapy emissions from that of any other known device, and rightly asked for clinical studies to be carried out in the first development phase until there was a revised version. This was done via a "peer review" process that analyzed 2393 cases (Table 1) related to chronic and noncancer and oncological pain resistant to other treatments.

The characteristic that called for an in-depth analysis by FDA experts was that of a new electrostimulation parameter used in humans, given that Scrambler Therapy is different from the theoretical and technological development of conventional TENS devices. As a result, the FDA approved Scrambler Therapy as a noninvasive electro-analgesia device, but in the review process, acknowledged its unique feature, which drastically differentiates it from conventional TENS devices. Table 2 summarizes the main differences.

For this reason, it is correct to refer to this new methodology by clearly and uniquely defining it only as Scrambler Therapy, both in the scientific literature and in clinical practice.

Table 1. Preliminary Data Submitted to FDA Analysis Before Marketing.

Sponsor	Objectives	Methodology	N	Diagnosis and Main Criteria for Inclusion	Criteria for Evaluation Efficacy	Criteria for Evaluation Safety	Efficacy Results	Safety Results
Policlinico Universitario Tor Vergata Università degli Studi di Roma Tor Vergata. Spontaneous study.	Effectiveness and short and long-term safety in patients with severe noncancer pain not responding to other treatments	Unblinded trial. Prospective study.	2297	High-grade neuropathy chronic pain (FBBS, Lumbosc., PHN, trigeminal, postsurgery, Brach. Plex, pudendum, low back pain, cervical-brachial). Drug resistant.	VAS scale	Medical visit during treatment and follow-up, questionnaire about undesired, side effects, global subjective impressions, also referred to particular sensations that cannot be better described.	Responders (pain relief >50%): 79.58% Partially responsive (pain relief 25%-50%): 11.64%	No undesired side effect has been pointed out or reported during treatment or on following control visits. Optimum compliance.
Osp. Umberto I° Frosinone Università degli Studi di Roma Tor Vergata. Spontaneous study	Effectiveness and short- and long-term safety in patients with severe cancer pain not responding to other treatments	Observational	33	Advanced-stage phase I cancer (palliative care), extremely high pain, drug-resistant pain	VAS scale, numeric, descriptive simple, daily patient diary about 24 hours (descriptive scale), reduction in the consumption of analgesia drugs	Medical visit, questionnaire about undesired, side effects, global subjective impressions, also referred to particular sensations that cannot be better described.	Responders (pain relief >50%): 100% pain relief 91.6% analgesic drugs: Complete reduction during cycle in 72% of cases. Strong reduction of dosing in the remaining 28%	No undesired side effect has been pointed out or reported. Optimum compliance.
Osp. Umberto I° Frosinone Università degli Studi di Roma Tor Vergata. Spontaneous study	Effectiveness and short- and long-term safety in patients with severe cancer pain not responding to other treatments	Observational	11	Advanced-stage cancer (palliative care), extremely high visceral pain, drug-resistant pain	VAS scale, numeric, descriptive simple, daily patient diary about 24 hours (descriptive scale), reduction in the consumption of analgesia drugs	Medical visit, questionnaire about undesired, side effects, global subjective impressions, also referred to particular sensations that cannot be better described.	Responders (pain relief >50%): 100% Complete reduction during cycle in 81.8% of cases. Strong reduction of dosing in the remaining 18.2%	No undesired side effect has been pointed out or reported. Optimum compliance.
[IRCCS] Fondazione Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena, Milano. Spontaneous study.	Effectiveness and short- and long-term safety in patients with severe noncancer pain not responding to other treatments	RCT vs multidrug therapy (amitryptyline + oxycodone + clonazepam). Two-armed control study. Unblinded trial. Prospective study	52	High-grade neuropathy chronic pain certain/putative (postsurgical neuropathic pain, postherpetic neuralgia, narrow canal syndrome)	VAS scale, reduction in the consumption of analgesia drugs	Medical visit during treatment and follow-up, questionnaire about undesired, side effects, global subjective impressions, also referred to particular sensations that cannot be better described.	Analgesic consumption at 3 months from the last treatment with Scrambler Therapy decreased by −71.9% compared with an initial, −67.7% with opiate doses, by −71.9% in anticonvulsants and by −57.3% in antidepressants.	No undesired side effect has been pointed out or reported during treatment or on following control visits. Optimum compliance.

Abbreviations: VAS, visual analogue scale; RCT, randomized controlled trial PHN, postherpetic neuralgia; FBBS, failed back surgery syndrome.

Table 2. Main Differences Between Transcutaneous Electrical Nerve Stimulation (TENS) and Scrambler Therapy.

Reference	TENS	Scrambler Therapy
Active principle	Pain transmission inhibition	"No pain" information
Theoretical model	Gate control theory	Scrambler therapy
Target	A-Beta fibers (nerve)	Surface receptors of C fibers (dermatomes)
Emission	Linear pulse (typically square wave), 30-150 mA	Dynamic neuronal synthesis (maximum 5.5 mA)
Main indications	Acute pain, muscle-skeletal pain, physiotherapy	Chronic neuropathic and cancer pain, opioid resistant pain. Scrambler therapy may be used in multiple settings, including hospitals, pain management clinics, and inpatient hospice units
Restrictions on use	None	Use restricted to physicians, or other qualified health care professionals under their direct supervision
Analgesic tolerance	Frequent	No
Technology	Generator with frequency and variable pulse width (modifiable by the operator)	Artificial neurons (emission not modifiable by the operator)

Interactions With Drug Treatments

Anticonvulsants used for pain control (especially in high dosages) may inhibit Scrambler Therapy effectiveness due to their interference with action potentials. Therefore, it is recommended that patients be weaned from them prior to or during the initial Scrambler Therapy treatments. It also appears that ketamine blocks the analgesic efficacy of the treatment. It is not known how long this inhibitory effect lasts after ketamine is stopped. Similar concerns exist for other local anesthetics and muscle relaxants.

Minor side effects such as muscle weakness or hypotension seem to occur or may worsen when Scrambler Therapy is used along with muscle relaxants, while local anesthetics seem to decrease Scrambler Therapy effectiveness. These warnings are included in the medical device documentation, recorded in the FDA and CE marketing authorization procedure.

Procedures to Verify the Efficacy and Safety of Treatment

Treatment outcome is highly dependent on the operator's ability to correctly identify electrode positioning areas and to fine-tune stimulation intensity. The key to the pain system remodulation process achieved by Scrambler Therapy is the ability to completely eliminate the pain (or at least get it to < 2/10) during each treatment session, without the patient feeling any significant discomfort from the stimulation.

Criteria to Increase the Duration of the Treatment Cycle or Early Termination

The treatment cycle consists of 5 daily sessions for 2 consecutive weeks. The treatment can be stopped earlier if the patient is completely pain-free for 24 hours after the last treatment. Further treatment is not indicated in a pain-free patient.

Conversely, the planned 10-day cycle duration should be prolonged with the same normal frequency when:

- Weaning from drugs that might interfere with Scrambler Therapy (see notes on drugs)
- The patient continues to show clear signs of improvement with the extension of the treatment time.

The Importance of the Electrodes

Optimally, electrocardiography (EKG) electrodes with spongy contact surfaces are recommended for use (Figure 5). The use of different electrodes may decrease the effectiveness of Scrambler Therapy due to the distortion of information. This may make the Scrambler Therapy treatment more uncomfortable and may prevent a successful fine tuning of the electrode stimulation. It is especially not recommended to use "large" electrodes, like the ones usually used for TENS. In this case, apart from the problems previously listed, the broad electrode surface may stimulate incorrect areas because of poorly selective recruitment. This could lead to a pain increase during or after the treatment. In addition, the different impedance of these electrodes may cause continual intervention of the device protections. This tends to "cut" the output emissions, producing a distortion of the information. Electrodes should not be reused, as this may impair the ability of Scrambler Therapy to transmit information and may cause skin irritation. A small amount of gel should be added to the center of the electrode in order to optimize conduction.

Appropriate Training of Scrambler Therapy Operators

Training is one of the fundamental conditions for the correct usage of Scrambler Therapy in clinical research or hospital practice. International primary training is held (free of

Figure 5. Electrocardiography (EKG) electrodes recommended.

charge) in public hospitals in Italy (Rome). The training course is for clinical researchers and physicians who will themselves become trainers in their country of origin. Apart from addressing issues pertaining to the correct methodology usage, the training clarifies scientific and methodologic issues in clinical research.

Secondary training is provided by the countries that have medical personnel who have undergone primary training. It is aimed exclusively toward correct method of use in clinical practice. Like most clinical practice procedures, the device usage instructions do not replace an adequate course of training, which normally lasts for 3 days.

Scrambler Therapy Data Manager

To solve or reduce problems of lack of data uniformity and operator dependent bias, a free dedicated software, Scramble Therapy Data Manager (STDM), was developed to be used together with the Scrambler Therapy. STDM can support clinical trials to reduce operator-dependent bias to a minimum. STDM is fully compliant to HIPAA (Health Insurance Portability and Accountability Act) and GDPR (General Data Protection Regulation) privacy standards. To use STDM, the daily data of each treatment are documented during the treatment. After the daily treatment, the operator can immediately check if the application was successful and receive information to help improve subsequent treatments. This immediate feedback allows the operator to take corrective action before the Scrambler Therapy course is completed, reducing or eliminating errors. All the Scrambler Therapy users can request for free this software from the Scrambler Therapy official scientific and clinical information site.

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	80.00
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	50.00
8	6.15	0.53	13	92.30
9	8.15	1.68	19	84.21

Abbreviation: NRS, Numeric Rating Scale (pain).

Independent Clinical Trials

In 2009, the Scrambler Therapy device was marketed in the United States. This enabled independent clinical trials to evaluate the efficacy of Scrambler Therapy for neuropathic and cancer pain. One can notice a broad variability in success outcomes due to different operator experience, and in some cases only a partial compliance to the recommended treatment approach. One can certainly state that, in patients with chronic pain, the placebo effect can play an important role. However, statistically, treatment efficacy (pain relief >50%) of Scrambler Therapy is typically around 80% in the scientific publications of researchers who have a broader experience in the method and are completely compliant to the standard protocols. This is also the general data that emerge from the studies with the highest number of patients enrolled. The comparative references of all the studies analyzed are available in Table 3.

In 2015, Compagnone et al[7] published the only multicenter study involving a large case series of patients (201). The study included 9 pain centers with heterogenous experience on Scrambler Therapy use. The different clinical results strongly related with these differences are documented in Table 3.

A further analysis of this study extrapolated the data of patients in whom the pain was correctly zeroed during each treatment. These data confirm that complete pain relief 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 to obtain the maximum success rate, during the initial and follow up treatments.

This study also highlighted that, within the same team, more experienced practitioners achieved complete pain resolution during treatment in patients where other less experienced operators had failed.

In the absence of randomized controlled trials (RCTs) versus sham correctly performed on a wide range of cases,

Table 4. Summary Clinical Data of All Articles Published Prior to October 31, 2018.

First Author/Year	Trial Type	N	Diagnosis	Results	Source of Bias	Comments
Han JW, 2018[11]	Observational	1	Low back pain, depression	VAS score decreased from 8 to 1. The Beck Depression Inventory score decreased from 22 to 7.	Unblinded, small sample size	
Fabbri L, 2018[12]	Observational	1	Phantom limb pain	VAS score decreased from 7 to 0. Follow-up: visit after 15 days of treatment till 2 months demonstrated a maintenance of pain absence.	Unblinded, small sample size.	
Warner NS, 2018[13]	Observational	1	Amyloid neuropathy	Substantial pain reduction	Unblinded, small sample size.	
Tomasello C, 2018[14]	Prospective	9	CIPN	VAS score decreased from 9.22 to 2.33 (10 days of Scrambler Therapy) and from 9.22 to 0.11 at the end of the optimized cycle tailored for each patient. Changes in drug consumption of analgesic drugs: Opioids: -85.22% from initial dosage. Anticonvulsants: 93.78 % from initial dosage, The follow-up was evaluated for time intervals of 1, 2, 3, and 6 months or more after the EOC. Because of disease recurrence, follow-up was reduced to 1 month in 2 patients, at which time pain was absent in both. The remaining 7 patients continued to report no pain throughout the follow-up period. Only 1 patient was in need of a quick recall of a cycle of five applications at 7 months after the first treatment cycle; after 1 year from the return cycle, the patient was still without pain.	Unblinded, small sample size.	The optimized cycle tailored for each patient is compliant with standard protocols and methodology usage.
D'Amato SJ, 2018[15]	Observational	1	Chronic central pain	Pain reduction from 9-10/10 to 0-0.5/10, then 5 more sessions a month later. Baseline pain stayed at 2/10 at 140 days with spikes only to 5/10, and no additional medications.	Unblinded, small sample size.	
Park HS, 2018[16]	Observational	1	Neuropathic pain related to leukemia in a pediatric patient	During treatment, the NRS score decreased from 8/10 to 3/10 after the first session. Subsequent sessions were followed by marked improvement of pain: after 3 treatment sessions, NRS score was 0/10. Following pain reduction, drugs were progressively reduced and then prescribed at need. No other treatment sessions were performed. No adverse events were observed. Pain intensity was investigated 1 and 4 weeks after completion of treatment: the patient referred to no pain.	Unblinded, small sample size.	
Maureen A, 2018[17]	Observational	1	Central neuropathic pain in a patient with transverse myelitis	The patient failed multiple drug trials for treatment of the pain. Following a course of Scrambler Therapy, pain scores improved considerably more than what was reported with previous pharmacologic and non-pharmacologic interventions.	Unblinded, small sample size.	Incomplete outcome data.
Smith TJ, 2018[18]	Prospective	10	Postherpetic neuropathy (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.	Unblinded, small sample size. The coauthor (Marineo G.) developed the Scrambler Therapy basic and applied research and is the owner of patents on technology application.	
Kim YN, 2017[19]	Observational	1	Shingles	Prior to pain Scrambler Therapy, the mean VAS score was 7 points; this reduced to 1 point after completion of 10 therapy sessions. The average quality of life score before pain Scrambler Therapy was 102 points; this increased by 128 points after the 10 therapy sessions had been completed.	Unblinded, small sample size. Incomplete data.	
Kashyap K, 2017[20] Erratum[21]	Prospective	20	Cancer pain not responding to oral analgesics	Patients were scheduled to undergo a total of 12 sittings of Scrambler Therapy, 10 cycles on consecutive days and 1 each at the 2 follow-up visits after 1 week each. 10 tr.:VAS score decreased from 7.50/10 to 0.75/10. First follow up (1 tr.): VAS score decreased from 2.05/10 to 0.45/10. Second follow-up (1 tr.): VAS score decreased from 1.15/10 to 0.15/10	Unblinded, small sample size.	
Smith T, 2017[22]	Observational	3	Chronic postmastectomy pain	All patients had marked (>75%) and sustained (months) reduction of allodynia, hyperalgesia, and pain. All reported marked improvements in their quality of life and normal function.	Unblinded, small sample size.	
Smith T, 2017[23]	Observational	1	Human immunodeficiency virus–related peripheral neuropathy	Pain rapidly improved, as did motor and sensory function, with just four 45-min treatments. The patient was able to come off opioids for the first time in years. When his pain returned 6 months later, only 2 treatments were needed to resolve it.	Unblinded, small sample size.	

(continued)

Table 4. (continued)

First Author/Year	Trial Type	N	Diagnosis	Results	Source of Bias	Comments
Notaro P, 2016[24]	Prospective	25	Pain induced by bone and visceral metastases and refractory to standard therapies. In 17 patients (68%), chronic pain was related to bone metastases (82% from solid tumors and 18% from hematologic malignancies), and 8 cases (32%) suffered from pain due to primary tumor (37.5%) or visceral metastases (62.5%).	After 10 days of Scrambler Therapy, pain score significantly reduced from 8.4 ± 1.4 to 2.9 ± 1.5 (P = .008), showing a constant and significant decrease during the whole treatment (ANOVA P = .0001). At the end of Scrambler Therapy, the mean pain relief recorded was 89%. A reduction in pain from baseline ≥50% obtained by the treatment lasted between 4 to 24 weeks (mean pain decrease duration was 7.7 ± 5.3 weeks).	Unblinded, small sample size.	Scrambler therapy standard usage in cancer pain should be in line with the patient's needs, also after the initial 10 treatments. The aim is to keep the cancer pain constantly under control.
Raucci U, 2017[25]	Observational	4	Complex regional pain syndrome.	Prior to Scrambler Therapy, the patients were treated with conventional pharmacological therapy and nonconventional treatments without any relief. The pain score ranged from 7 to 10 on the NRS scale at the beginning of Scrambler Therapy. The pain intensity diminished, and complete relief was obtained after 7 to 12 days in all the patients. In addition, they noted a significant improvement of quality of life with complete functional recovery. They all returned to their usual daily activities and developed normal sleep patterns. Hypotonia of the right foot persisted in Patient 2. When followed up after 6 to 21 months, the patients did not need any medication and were free from pain. Patient 2 had a 1-year relief of her pain but returned for a mild pain in her right knee at the site of a scar. She was treated with local neural therapy and had complete disappearance of the pain.	Unblinded, small sample size.	
Lee SC, 2015[26]	Open-label	20	CIPN (n = 6), neuropathic pain by metastatic bone lesion (n =7), and postsurgical neuropathic pain (n= 7).	Average NRS pain score; CIPN: 6.1 to 2.6 (3.1 one month) Metastatic bone pain: 7.4 to 3.0 (3.1 one month) Postsurgical pain: 8.5 to 3.7 (5.1 one month)	Unblinded, small sample size. Unclear learning curve.	
Starkweather AR, 2015[27]	Double-blinded, randomized controlled trial	30	Persistent nonspecific LBP	In the treated group, 7 (47%) participants had a >50% reduction in the "worst" pain score from baseline to the 3-week follow-up visit, 5 (33%) participants had a 30%-49% reduction, and 3 (20%) had a 20%-29% reduction.	A complete double-blind prevents the operator to follow the normal procedures. This can erase or certainly extremely reduce the efficacy of the treatment. The stimulation of the sham was too close to the pain area. This may imply partial analgesic efficacy.	Clinical trials with significant deviations from standard protocols and methodology usage.
Pachman DR, 2015[28]	Prospective	37	CIPN	25 patients were treated primarily on their lower extremities while 12 were treated primarily on their upper extremities. There was a 53% reduction in pain score from baseline to day 10; a 44% reduction in tingling; and a 37% reduction in numbness. Benefit appeared to last throughout 10 weeks of follow-up. There were no substantial adverse events.	Unblinded	
Moon JY, 2015[29] Comment[30]	Prospective	147	Various pain conditions	A successful outcome was predefined as >50% pain relief on a 0-10 numerical rating scale that persisted for longer than 1-month after the last treatment. The success rate was 38.1%.	Significant deviations from standard protocols and methodology usage	
SA Kim, 2015[31]	Observational	3	1. Chronic inflammatory demyelinating polyneuropathy. 2. Transverse myelitis 3. Multiple old compression fracture due to senile osteoporosis	Case 1: VAS score from 9/10 to 2/10. Six months later, VAS score was 3/10. Case 2: VAS score from 9/10 to 2/10. Three months later, VAS score was 4/10 and the frequency and intensity of abrupt pain attack was decreased to 50%. Case 3: VAS score from 8/10 to 5/10. Four weeks later, VAS score was 5/10.	Unblinded, small sample size.	
Compagnone C, 2015[7]	Multicenter retrospective analysis	201	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.	The difference between pretreatment NRS 7.41 (SD 2.06) and posttreatment 1.60 (SD 2.22) was statistically significant (P < .0001). 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, NSAIDs were eliminated in 25 of 28 (89.28%) cases. Long-term outcome (3 months) was evaluated with changes in the BPI scale. There is an improvement in each point evaluated. The greatest modification is in the Pain, Sleep, and Work items. The Pain Score at entry has been reduced from 7.41 (SD 2.06) to 3.7 (SD 1.4).	Unblinded	
Coyne PJ, 2013[32]	Prospective	39	CIPN, other chronic pain syndromes, including chemotherapy-induced peripheral neuropathy with predominant numbness but not pain; postmastectomy pain; postsurgical pain; postherpetic neuropathy; Postradiation pain; or others such as vertebral compression, fracture, miscellaneous.	39 patients, mean age 56.5 years, 16 men and 23 women, were treated over an 18 month period for an average of 9.3 days each. The "now" pain scores reduced from 6.6 before treatment to 4.5 at 14 days, 4.6, 4.8, and 4.6 at 1, 2, and 3 months. (P < .001) Clinically important and statistically significant improvements were seen in average, least, and worst pain; BPI interference with life scores, and motor and sensory scales on the EORTC CIPN-20.	Unblinded, only partially complies to standard protocols and methodology usage. The Numeric Rating Scale for "pain now" immediately before and after each session seems to indicate an insufficient learning curve.	The standard training courses in 2013 were available only in Italy.

(continued)

Table 4. (continued)

First Author/Year	Trial Type	N	Diagnosis	Results	Source of Bias	Comments
Ko YK, 2013[33]	Observational	3	Postherpetic neuralgia	Case 1: VAS score from 7/10. to 3/10. The electric shock-like pain disappeared completely. Four weeks later, VAS score was 3/10. Case 2: VAS score from 6/10 to 2/10. The electric shock-like pain disappeared completely. Four weeks later, VAS score was 3/10. Case 3: VAS score from 6/10 to 2/10. The electric shock-like pain disappeared completely. Four weeks later, VAS score was 3/10	Unblinded, small sample size.	
Park HS, 2013[34]	Observational	3	Cancer pain	Case 1: VAS score from 8/10 to 3-3.5/10. Pain relief continued for 2 months. Case 2: VAS score from 8/10 to 2/10. NRS score 2.5/10 was maintained for approximately 2 weeks after treatment. Case 3: VAS score from 6/10 to 2/10. After 10 sessions of Scrambler Therapy, the NRS score has been maintained at 2/10, and the pain area maintained at about 80% reduced state, for 2 months.	Unblinded, small sample size.	
Ricci M, 2012[35] Comment[36]	Open-label	73	Chronic pain	Mean pain value at T0 (pretreatment value) was 6.2 [± 2.5 SD (standard deviation)], 1.6 (±2.0) ($P < .0001$) at T2 (after the 10th day of treatment), and 2.9 (±2.6) ($P < .0001$) at T4 (after the second week of follow-up, ie, 1 month after the beginning of treatment). Response after the second week of treatment showed a clear reduction in pain for both cancer (mean absolute delta of the reduction in NRS value = 4.0) and non-cancer (mean delta = 5.2) patients. The pain score had decreased by 74% at T2.	Unblinded	
Sparadeo F, 2012[37]	Clinical practice	91	Variety of pain syndromes, including CRPS, spine pain, neuralgias (such as postherpetic or postchemotherapy), and multifocal pain problems	Marked pain reduction. BPI scores at 3 to 6 months of follow-up were reported to be improved by more than 50%.	Insufficient data for accurate analysis.	
Ghatak RK, 2011[38]	Open label	8	Low back pain	VAS score decreased from 8.1/10. to 3.6/10. Pain relief continued for 2 months. Reduction of Oswestry disability index from baseline value of 49.875 (24-68) to a value at the end of treatment was 18.44 (6-40) this when pared and compared was found to be statistically very significant ($P < .0001$)	Unblinded, only 6 treatments performed (normal cycle 10 treatments or more)	
Marineo G, 2011[39]	RCT	52	Postsurgical neuropathic pain, postherpetic neuralgia, spinal canal stenosis	The mean VAS pain score before treatment was 8.1 points (control) and 8.0 points (scrambler). At 1 month, the mean VAS score was reduced from 8.1 to 5.8 (−28%) in the control group, and from 8 to 0.7 points (−91%) in the scrambler group ($P < .0001$). At 2 and 3 months, the mean pain scores in the control group were 5.7 and 5.9 points, respectively, and 1.4 and 2 points in the scrambler group, respectively ($P < .0001$). Opioids were totally eliminated in 11 of 17 cases, halved in one case, and unvaried in 5 cases. Anticonvulsants were eliminated in 17 of 24 cases, reduced in one case, and unvaried in 6 cases. Antidepressants were eliminated in nine of 19 cases, reduced in 4 cases, and unvaried in 6 cases.	Unblinded, Marineo G. developed the Scrambler Therapy basic and applied research and is the owner of patents on technology application.	
Smith TJ, 2010[40]	Prospective	16	CIPN	The pain score fell 59% from 5.81 before treatment to 2.38 at the end of 10 days ($P < .0001$ by paired *t* test). Four patients had their CIPN reduced to zero. A repeated-measures analysis using the scores from all 10 days confirmed these results.	Unblinded, small sample size.	
Sabato AF, 2005[41]	Prospective	226	Failed back surgery syndrome, sciatic and lumbar PHN, trigeminal neuralgia, postsurgery nerve lesion neuropathy, pudendal neuropathy, brachial plexus neuropathy, LBP, others	The total results show 80.09% of responders (pain relief>50%), 10.18% of partially responders (pain relief from 25% to 49%) and 9.73% of no responders (patients with pain relief <24% or VAS > 3)	Unblinded. The coauthor (Marineo G) developed the Scrambler Therapy basic and applied research and is the owner of patents on technology application.	
Marineo G, 2003[5]	Prospective	11	Advanced stage cancer patients (3 pancreas, 4 colon, 4 gastric) suffering from elevated drug-resistant visceral pain.	VAS score decreases from 86/100 to 1.5/100. During the reference period, nine out of eleven patients (81.8%) are seen to have stopped requesting painkillers between the second and the fifth treatment session. The remaining 2 patients (18.2%) considerably reduced their dosage and undertook mild therapy. In view of the possible application of the method at the patient's home, an assessment was made of how often treatment would be required to maintain optimal pain control. Right from the first treatment session, 7 patients (63.6%) were able to get by on a single treatment session every 24 hours or more, a percentage that rose to 90.9% by the end of the cycle. The remaining patient (9.1%) is situated in a window in which an average of 2 treatment sessions are required every 24 hours. Effectiveness unchanged until the natural conclusion of the disease.	Unblinded, Marineo G. developed the Scrambler Therapy basic and applied research and is the owner of patents on technology application.	Scrambler therapy standard usage in cancer pain should be in line with the patient's needs, also after the initial 10 treatments. The aim is to keep the cancer pain constantly under control.

Abbreviations: VAS, visual analogue scale; CIPN, chemotherapy-induced peripheral neuropathy; NRS, Numeric Rating Scale; PHN, postherpetic neuropathy; LPB, low back pain; BPI, Brief Pain Inventory; CRPS, complex regional pain syndrome.

it is important to understand at least indicatively how much the power of suggestion (placebo, hypnosis) can explain the clinical results of Scrambler Therapy. In this context, from what emerges in the reference clinical trials, not even powerful forms of conditioning such as hypnosis can completely eliminate pain during the treatment in a systemic manner.[8] Conversely, the immediate ability to eliminate the pain in each treatment, in addition to being one of the peculiar characteristics of the Scrambler Therapy, is the primary index of the correct execution of the therapy.[9]

Currently, independent researchers are more carefully assessing the bias issue. There has been a great improvement in the quality of recent publications, and standardization of clinical trial success outcomes.

In the near future, Scrambler Therapy needs further randomized clinical trials versus sham or other treatments, to result in a more general acceptance of it. However, the proper use of Scrambler Therapy, being operator-dependent, allows only for a partial double-blind or single-blind trial design. Attempts to do a complete double-blind clinical trial automatically cause substantial changes in the standard treatment protocol, which requires substantial patient interaction to determine proper placements of electrodes and intensity of treatment. These changes prevent the operator to follow the normal procedures registered in the healthcare authorizations and can erase or significantly reduce the efficacy of the treatment, consequently invalidating the scientific data.

Analysis of the Clinical Trials

All the publications in English-language scientific journals concerning the use of Scrambler Therapy in chronic neuropathic pain and cancer pain have been included in this analysis. The research was carried out in the databases from PubMed/Medline, Cochrane Library, and Google Scholar. Search terms included "Scrambler Therapy" and/or "Calmare" to identify all articles published prior to October 31, 2018.

Using these selection criteria, 30 articles (with studies of varying scientific quality, type, and completeness of analysis) were identified.

Extrapolated data for each publication (trial type, number of patients, diagnosis, results, and source of bias) are provided in Table 4. Where possible, compliance with standard usage protocols was also examined in the comments. Compliance with standards means compliance with all the procedures for the correct use of the Scrambler Therapy device described in the user manual. More information is also available in the recommendations on the Scrambler Therapy official scientific and clinical information site.[10]

All studies show the absence of any substantial side effects and report different degrees of efficacy.

The most important source of bias, common to all studies, is the operator dependent variability. Other bias sources are documented separately.

Verification of the Theoretical Model

All theoretical models need an experimental test that must produce outcomes in line with foreseen expectations. Until today, the published studies and clinical routine experience have confirmed the expectations of the Scrambler Therapy theory model. More in-depth validation will be achieved through neuroimaging to better highlight related plasticity phenomena, and also from studies of central pain. In waiting for further validation by independent studies, some basic points have been relatively well established:

- Currently, we are aware that C fiber excitation produced by Scrambler Therapy is not compatible with the gate control theory. Electrical C-fiber excitation without information (ie, simple electrical impulses not encoded as "non-pain "information) should produce pain, whereas, in line with theoretical expectations of "non- pain" information emission, Scrambler Therapy rapidly produces analgesia. The rapidity of the analgesic response (typically immediate absence of pain when adjustment is complete) tends to exclude the mediation of endogenous analgesic molecules in favor of the effect of information, which by its nature is immediate. These elements experimentally support the expected effects of synthetic information of no pain.
- The effectiveness of a treatment cycle depends on the stability of the underlying neurological damage. If the neurological damage is stable, the treatment of effects tends to be decisive. On the other hand, if the neurological damage is progressive pain relapse may occur.[14,39]
- This is consistent with the hypothesis of controlling the effects of plasticity in chronic pain (not present in acute pain) through information control.
- Contrary to other forms of electro-analgesia, development of resistance to Scrambler Therapy is unknown. Based on clinical experience each new treatment cycle fully maintains its efficacy and overall requires fewer treatment sessions than the initial one.[22,23]
- This aspect is consistent with the theoretical model. If the emission of artificial neurons is really recognized as "self," it cannot create resistance phenomena.
- Higher clinical efficacy is seen in chronic persistent pain with meaningful neuropathic implications (present also with oncological pain), which typically is not responsive to other treatments.

- This aspect is consistent with the remodulation hypothesis of the pain system due to the effect of "non-pain" information. Similarly, in physiologic/acute pain, where plasticity[42,43] is not meaningful, Scrambler Therapy behaves simply as a symptomatic therapy used when needed. This double aspect of efficacy is also consistent with theoretical expectations.
- To produce a total and immediate analgesic effect by Scrambler Therapy, it is sufficient for the patient to feel a circumscribed stimulation below the area of the electrodes, which are of reduced dimensions (EKG single-use type). It is therefore not necessary to feel the stimulus in the pain area or areas of paresthesia. This result is consistent with the transmission of information of "non-pain," and not with information blockage.
- Immediately after the treatment, no type of paresthesia or anesthesia is recorded. The physiological response to evoked pain remains unchanged, notwithstanding the clear analgesic effects on chronic pain. This result tends to rule out a prolonged period of C-fiber refractoriness and plays in favor of the remodulation of the pain system's response carried out by synthetic information of "non-pain," as assumed in the theory.
- In the conventional electro-analgesia TENS systems currently known it is necessary to exclude C fiber stimulation, since electrical stimulations might provoke pain. This is the reason why conventional TENS, notwithstanding other stimulation features (frequency, intensity, modulation, burst) rarely provides maximum pulse width higher than 250 microseconds. The ability of Scrambler Therapy to constantly operate with impulses suited to stimulate C fibers offers confirmation that it is different from the gate control therapy and from analgesia limits produced by conventional TENS.[44]
- For involuntary or voluntary conditionings in pain reduction, broad scientific literature on the analgesic effect of placebo and hypnosis shows pain relief far lower than the ability of Scrambler Therapy to eliminate or markedly reduce pain during treatment. Regarding the effects of hypnosis (the most extreme type of conditioning), the applications in clinic are varied, but the number of publications that specifically treat chronic neuropathic and cancer pain is very low.[45]

In this context, it is important to remember that Scrambler Therapy has been specifically studied for patients with high intensity pain, not responsive to any treatments (in particular nonresponsive to opioids), and it is for this reason a basically autonomous pain treatment. All these specific characteristics make the comparisons between hypnosis and Scrambler Therapy difficult for type of pain, severity, lack of response to protocol treatments, chronicity, reduction of drug therapies. However, some reference studies may be indicative to carry out a rough assessment, even if with the limits set out.

In 2018, Juel et al[46] published a small study on hypnosis as a complementary treatment conducted on 4 cases of abdominal pain from chronic pancreatitis. Three patients completed the study achieving a short-term pain relief in the range of 20% to 39% compared with baseline.

In 2003, Marineo[5] published a study on eleven terminal cancer patients (3 pancreas, 4 colon, 4 gastric) suffering from elevated drug-resistant visceral pain (see Table 3). In this case, the VAS average dropped from 9.1/10 to 0.7/10 (pain relief 92%). Nine (81.8%) of the patients suspended pain-killers within the first 5 applications, while the remaining two (18.2%) considerably reduced the dosage taken prior to Scrambler Therapy. There is a potential conflict of interest because Marineo is the researcher who developed Scrambler Therapy. However, independent studies performed subsequently (Table 3) confirm the possibility of radically breaking down cancer pain and significantly reducing or completely eliminating the analgesic drugs, confirming the results of Marineo's pilot trials.

In 2018, Keil et al[47] published an observational study on 30 chronic pain patients (17 patients without hypnosis, 13 patients with hypnosis). The analysis of the pain intensity assessed with the Numeric Rating Scale did not show statistical significance ($P > .05$).

In 2017, Wortzel and Spiegel[45] published a review on the effects of hypnosis in cancer care. Regarding chronic cancer pain, the review refers to 2 articles: The first, from 2009 by Butler et al,[48] is a randomized clinical trial that examines the effects of group therapy with hypnosis (supportive-expressive group therapy) plus education compared with an education-only control condition on pain over 12 months among 124 women with metastatic breast cancer. The conclusion at the end of the study is,

> Intention-to-treat analyses indicated that the intervention resulted in significantly less increase in the intensity of pain and suffering over time, compared to the education-only group, but had no significant effects on the frequency of pain episodes or amount of constant pain, and there was no interaction of the intervention with hypnotizability.

The other study, from 1983 by Spiegel and Bloom,[49] on 54 women with metastatic carcinoma, concludes,

> Pain frequency and duration were not affected. Changes in pain measures were significantly correlated with changes in self-rated total mood disturbance on the Profile of Mood States and with its anxiety, depression, and fatigue subscales.

The large number of RCT versus placebo studies showed many more specific data on these effects. However, according

to emerging scientific literature, the placebo effect also falls short of systematically eliminating or drastically reducing the pain such as the Scrambler Therapy in the treatment of chronic neuropathic or cancer pain.[50-52]

There is, however, a general agreement that the placebo/nocebo effect is extremely changeable on the basis of numerous variables. We are also quite far from being able to accurately determine an exact evaluation of placebo effect magnitude. For example, in acute pain, the placebo effect cannot be separated from the decrease in pain due to the normal healing process. Sensitivity to placebo also varies from person to person, as well as the possibility of turning into nocebo. In short, the scientific discussion on the placebo / nocebo effect, and the possibility to determine exactly the magnitude of the effect in the various types of pain and in the various possible study conditions, is still very open.[53,54]

Discussion

Chronic pain is estimated to affect 100 million people in the United States alone, resulting in up to $635 billion in medical expenses and lost productivity each year.[55]

Chronic pain occurs in 19% (140 millions) of adult Europeans, seriously affecting the quality of their social and working lives. Historically, chronic pain treatment has certainly called for innovative solutions to overcome drug limitation that in this type of pain are not overall considered satisfactory and pose various tolerance and long-term side effect issues.[56-58] Thus, chronic pain is a major health care problem in Europe that needs to be taken more seriously.[59]

Cancer-related pain, reported by more than 70% of patients, is one of the most common and troublesome symptoms affecting patients with cancer. Despite the availability of effective treatments, cancer-related pain may be inadequately controlled in up to 50% of patients.[60]

Considering these points, one can easily understand why Scrambler Therapy has attracted much interest and has undergone spontaneous or institutionally sponsored clinical trials, despite having been developed without meaningful economic and marketing resources.

This is one of the main reasons for the qualitative limitations of the studies available on Scrambler Therapy. Most of the published studies are unblinded, do not have a control group, and can present numerous biases related to the different learning curves of the operators and / or the application of the standards provided for the optimal use of the treatment. Despite these limitations, the large case numbers collected to date indicate Scrambler Therapy efficacy and safety in many types of pain particularly difficult to manage and refractory to other types of treatment, although all this must to be confirmed with better quality studies.

The clinical trial on 2393 patients carried out at the University of Rome and presented to the FDA along with other smaller studies to evaluate the effectiveness and safety of the device can provide further useful indications of the operator-dependent variable. In this study, the treatment of patients was entrusted to physicians trained in pain therapy and replaced with new operators about every year. For this reason, a new phase of the learning curve occurred cyclically in this study. It is therefore reasonable to hypothesize that such a large series of cases carried out at different times by different operators, which also includes periodic learning curves, can in the future represent the average expectation of Scrambler Therapy success in chronic neuropathic pain in the normal hospital use.

Functioning Mechanism

The Scrambler Therapy functioning mechanism can be difficult to understand if interpreted only on mainstream concepts based on biochemistry and without other multidisciplinary elements. However, in medical science a multidisciplinary approach is ever-more widespread, and eventually also the Scrambler Therapy will be integrated in this process. One of the verifiable experimental consequences of this therapy is that types of chronic pain from the time perspective, but substantially acute in their manifestations (typically incidental pain due to mechanical causes that immediately disappears when returning to analgesic position), can have only a temporary response with Scrambler Therapy. In these cases, Scrambler Therapy is basically a symptomatic treatment that can be used "when needed," but will not necessarily produce medium- or long-term effects.

Instead, pain that is considered "difficult" to treat, persistent, nonresponsive or poorly responsive to pharmacological treatment is the most suitable for treatment with Scrambler Therapy. This type of pain is frequently characterized by altered cause/effect such as spontaneous persistent pain, allodynia, hyperalgesia, phantom limb, complex regional pain syndrome, or pain memory. Another consequence of the Scrambler Therapy theory that currently has been recorded in clinical practice is the possibility of treating effectively pain of central origin. Hopefully, in the future, specific clinical trials will be carried out in this regard.

Differences Between TENS and Scrambler Therapy

All forms of noninvasive electro-analgesia use weak electrical currents carried by surface electrodes. This often leads to the erroneous association of Scrambler Therapy with a more efficient form of TENS. Presumably the problem arises from the fact that the entire historical path of electroanalgesia has always had as its sole objective to block the transmission of pain through an electrical stimulus, regardless of the evolution of the technology used over time. In this sense, although TENS is supported for the first time by

a scientific rationale thanks to the theory of gate control, it is not an exception.

Scrambler Therapy interrupts this consolidated tradition by developing a new theoretical model of reference that has no precedent in its rationale, in the neurophysiological target used, in the mode of application, or in the optimal field of use in the clinic and introduces the technology of artificial neurons. In this sense, the only common point between TENS and Scrambler Therapy is related to the surface stimulation, therefore only the method of administration, remembering that also in this case Scrambler Therapy uses different targets and application methods.

Conclusion

As for the acceptance of Scrambler Therapy in health care systems, randomized trials are still necessary. However, the large preparatory case base for marketing and publications as of today suggests the validity of Scrambler Theory. For further recognition of the Scrambler Therapy autonomous theory model, we hope also to begin neuroimaging clinical trials and the treatment of central pain in the near future. Last, more standard outcomes in clinical trials will be possible by using the free STDM software. It allows collecting all data anonymously via ST-NET, an international network dedicated to Scrambler Therapy that enables to have a clear understanding of the clinical results in everyday use, and the patient's real experience.

Declaration of Conflicting Interests

The author declared following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The author developed the Scrambler Therapy basic and applied research and is the patent owner of the ST technology.

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