Pilot Study: Electrical Stimulation via the Scrambler Device as a Treatment for Restless Legs Syndrome/Willis Ekbom Disease

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Objectives: To evaluate, in a pilot fashion, efficacy and tolerability of electrical counter-stimulation using the Scrambler device in alleviating uncomfortable sensations and urge to move in patients with restless legs syndrome/Willis Ekbom Disease (RLS/WED).

Hypotheses: Electrical stimulation applied to the lower extremities using the Scrambler device will improve discomfort and alleviate urge to move in patients with RLS/WED. This form of therapy will be well-tolerated and without significant side effects.

Background Information:

Clinical Description of RLS/WED

Restless legs syndrome/ Willis Ekbom Disease (RLS/WED) is characterized by an unpleasant or uncomfortable urge to move the legs which comes on at rest and is at least partially alleviated by movement. Symptoms occur in the evening and nighttime hours[1]. It is estimated that 7.2% of the Western population has RLS/WED, with 2.7% of the population experiencing moderate to severe symptoms.

RLS/WED has a significant negative impact on quality of life and is associated with anxiety and depression. Patients often experience significant sleep fragmentation due to symptoms which leads to daytime sleepiness and fatigue, cognitive symptoms, and loss of productivity at work[2].

One-third of RLS/WED patients require daily pharmacologic therapy to manage symptoms[3]. Patients with refractory symptoms often require multiple drugs of different classes[4]. Adverse effects from the most common agents used in treating RLS/WED include: drowsiness, dizziness, unsteadiness, weight gain, depression, augmentation, and development of impulse control disorders[5-7].

Nonpharmacologic modalities are an important means of treating symptoms. Many nonpharmacologic strategies are based on counter-stimulation techniques to mask RLS/WED symptoms such as warm baths and massage. Sequential compression devices have been shown to be helpful in alleviating symptoms[8]. Nonpharmacologic counterstimulation modalities may be an important means of reducing medication burden in patients with RLS/WED and complementing pharmacotherapies in medically refractory patients.

Electrical Stimulation in the management of centrally driven neurogenic pain

Electrical stimulation has been utilized as an intervention in treatment of various forms of neurogenic pain (including peripheral neuropathy, trigeminal neuralgia, and multiple sclerosis). Much of the published data involves use of transcutaneous electrical nerve stimulation (TENS). TENS appears to work to reduce pain through both central and peripheral mechanisms. Animal and clinical studies demonstrate that the electrical impulses have a local effect on peripheral nerves to reduce pain at area of application. There also appear to be effects on central nervous system pathways (periaqueductal gray, medulla, and spinal cord) thus reducing pain at sites outside of the area of stimulation[9,10]. The opiate and GABA receptors are implicated in the effects of TENS. These receptors are also targeted by pharmacologic therapies commonly used in RLS management. There are no good data regarding the efficacy of TENS for RLS.

Scrambler Therapy is a specific form of electrical stimulation which has also been utilized in chronic neurogenic pain[11]. This modality of therapy differs from TENS in that the goal is to mediate the patient's perception of pain, rather than masking the peripheral pain signal. The results of this modality of treatment may be longer-lasting than TENS, presumably via reduction in central signal generation. Scrambler therapy works through C fibers to retrain the peripheral sensation in the area being treated. Further description of this technology is available at: International Patent PCT/IT2007/000647 and U.S. Patent No. 8,380,317. Literature search does not yield prior studies regarding efficacy of Scrambler therapy in treating RLS.

Multiple clinical trials have shown that electrical stimulation using Scrambler Therapy is an effective method of treating chronic neurogenic pain. Table 1 reviews the literature regarding the use of Scrambler Therapy in over 800 patients. Treatment is well tolerated and without significant side effects.

Electrical stimulation as a potential treatment of RLS/WED

Most patients with RLS/WED experience discomfort in the lower limbs which is described using terminology including: crawling, tingling, restless, electric, tension, and itching[12]. The peripheral discomfort localized to the lower extremities in RLS/WED appears to be driven by a central mechanism. Functional neuroimaging studies have elucidated that RLS/WED stems from striatal dopaminergic dysfunction[13,14]. This is corroborated by the positive response obtained when treating patients with dopaminergic medications[15]. The above data demonstrating efficacy of electrical

stimulation in other forms of centrally-mediated neurogenic pain, would suggest that this modality may also be an effective treatment in RLS/WED.

Significance: If electrical stimulation via Scrambler Therapy is effective in alleviating discomfort associated with RLS/WED, this may represent a novel nonpharmacologic modality of managing symptoms. Negative results will also be clinically useful in guiding strategies in the treatment of RLS/WED.

Proposed Study Design: Prospective, interventional, pilot study

Inclusion criteria:

- Male patients age 18 and over and post-menopausal women (or women who are not of child-bearing potential) diagnosed with RLS/WED by a board certified sleep medicine physician within the Mayo Clinic Center for Sleep Medicine.
- Patients must have moderate to severe symptoms which have been present for ≥ 3 months. Patients must endorse discomfort as part of their typical RLS/WED symptomatology.
- Patients must experience daily symptoms and must experience daily symptoms during afternoon hours (12-5 PM)
- Patients on no medications for RLS/WED, or those who have refractory symptoms despite RLS/WED medications will be enrolled. Patients on alpha-2-delta ligands (pregabalin, gabapentin) will be asked to discontinue these medications two weeks prior to starting treatments and remain off these medications throughout the study protocol.
- Informed consent to participate in this study needs to be obtained

Exclusion criteria:

- Research authorization not provided
- Patients who are asymptomatic (either by verbal report or completion of severity scale) at time of initiation of Scrambler Therapy treatment
- Patients who have made changes in medication regimen during the 2 weeks prior to study initiation (including initiation of iron supplementation)
- Prior use of Scrambler Therapy
- Female patients of child-bearing potential (those who are not post-menopausal or post-hysterectomy)
- Patients with implantable drug delivery systems, heart stents, or metal implants (including pacemakers and defibrillators)
- Patients with history of epilepsy or other medical conditions that in the opinion of the investigators should be excluded
- Patients with skin conditions or wounds in or around the area of electrode application (lower extremities)
- Patients treated with alpha-2 delta ligands (gabapentin, pregabalin), who cannot discontinue the medications as above

Proposed Methods:

A total of up to 10 eligible subjects will be recruited who have been diagnosed with chronic RLS/WED in the Mayo Clinic Center for Sleep Medicine. Subjects must experience daily symptoms and must typically be symptomatic during the timeframe in which Scrambler Therapy will be utilized (12-5 PM). Each patient will complete the International Restless Legs Syndrome Rating Scale (IRLS), a validated scale which assesses severity of RLS symptoms[16] at baseline (pre-treatment) and before and directly after each session of Scrambler Therapy.

Patients will receive Scrambler Therapy (Appendix VI) on a daily basis for up to 10 consecutive weekdays. Electrodes will be placed proximal to the area of RLS symptomatology, with gradual downward localization until the entire area of RLS symptoms has been treated. Treatment will initially take place on one leg. Treatments will be administered by a technician trained in using the Scrambler device. A physician or nurse (with familiarity of Scrambler therapy) will be available throughout each treatment session.

Patients will complete questionnaires regarding discomfort or other side effects encountered during or after treatment. They will also complete surveys assessing for any changes (benefits or worsening) in RLS symptomatology between treatments.

Patients will be monitored for any adverse events associated with the study procedures. Any reported adverse events will be expediently classified by the study group as to severity level, whether it relates to the treatments in the study protocol, and whether the event was expected or unexpected. This information will allow determination of whether or not the adverse event should be reported as an expedited report or part of the routinely reported outcomes data. All adverse events which meet criteria for expedited reporting will be reported to the institutional IRB as well as external agencies as required.

If there is no evidence of clinical benefit with the first 2-4 patients, then further patients may not be recruited.

Test schedule:

Tests and procedures	≤30 days prior to registration	Day 1, Prior to therapy	Daily for 10 consecutive week days beginning on Day 1 of active therapy	On last day of therapy	1 Week after last Session
Clinical visit with history and exam, Eligibility questions, Consent	X				
Baseline severity question confirming moderate to severe symptoms	X				
IRLS severity questionnaire regarding the prior week (Appendix I)		X		X	X
Patient Questionnaire: Just Before Each Treatment (Appendix II)		X	X		
Patient Questionnaire: Just After each treatment (Appendix III)			X		
Patient Questionnaire After each therapy and during weekly follow-up: Global Impression of Change and Patient Preference (Appendix IV)			X		
Daily Treatment Log and Adverse Assessment (Appendix V)			X		
Coordinator phone call to discuss therapy and any concerns, record any adverse events that are reported and to remind the patient to complete questionnaire and mail back					X

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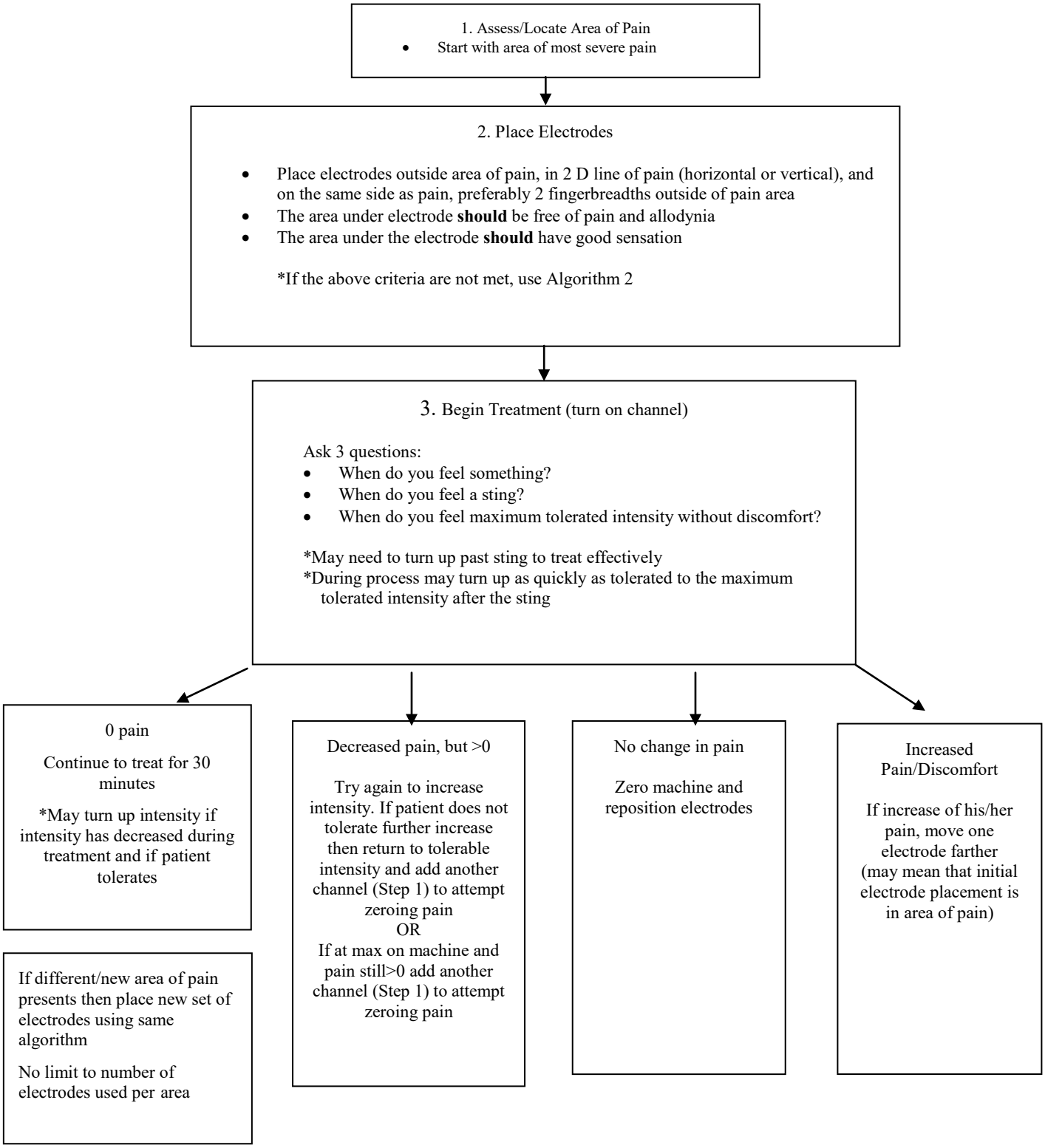
Table 1

	Reports, by first author	Year	Pt #	Condition	Results	Trial type	Comments
1	Marineo [17]	2003	11	Drug-resistant visceral pain	Substantial pain reduction	Prospective trial	
2	Sabato [18]	2005	226	multiple chronic pain syndromes	80% of patients with greater than a 50% pain reduction	Prospective trial	
3	Smith [19]	2010	18	Chemotherapy-induced neuropathy	Over 50% reduction in pain	Prospective trial	(16 evaluable)
4	Abdi [20]	2011	10	Back pain	28% reduction in pain.	Prospective trial	Abstract only
5	Marineo [21]	2011	52	post-herpetic neuralgia, spinal canal stenosis, and post-surgical neuropathic pain	Pain reduced more in Scrambler arm, than the control arm at 1 month and 3 months ((P<0.0001)	Randomized, controlled	Open label trial
6	Ricci [22]	2012	82	Various cancer and non-cancer pains	Mean pain scores dropped from 6.2/10 prior to treatment to 1.6 just after completing 10 treatment days to 2.9, 2 weeks after finishing treatment.	Prospective trial	73 evaluable pts.
7	Ghatak [23]	2011	8	Chronic low back pain	Pain score drop from 8.12 to 6.93; Drop in ODI from 49.88 to 18.44	Prospective trial	Open label
8	Sparadeo [24]	2012	173	Chronic pain >6 months	Marked pain reduction	Clinical practice experience	91 provided 3-6 months f/u
9	Coyne [25]	2013	39	Cancer pain syndromes, including Chemotherapy-induced neuropathy	Significant pain reduction with 10 treatment days that largely lasted for 3 months	Prospective trial	
10	Smith [25]	2013	10	Post-herpetic neuralgia	95% pain reduction, that largely lasted for 3 months	Prospective trial data	Some pts were the same as in a previous trial [18]
11	Ko [26]	2013	3	Post-herpetic neuralgia	Marked pain reduction	Clinical practice experience	
12	Park [27]	2013	3	Cancer bone metastases	Marked pain reduction	Clinical practice experience	
13	Campbell [26]	2013	14	Chemotherapy-induced neuropathy	No differences between active and placebo arms	Prospective, double-blind, placebo-controlled trial	Abstract only

	Reports, by first author	Year	Pt #	Condition	Results	Trial type	Comments
14	Pachman [28]	2014	37	Chemotherapy-induced neuropathy	Average pain decreased by 53% at end of treatment and benefit largely remained for 10 weeks after completion.	Prospective trial	Decrease in tingling and numbness, too.
15	Sparadeo [29]	2014	91	Variety of pain syndromes	Substantial pain reduction	Clinical practice experience	Consecutive patients; Some pts were the same as in a previous trial[30]
16	Moon [30]	2014	147	Variety of pain syndromes		Clinical practice experience	
17	Starkweather [31]	2015	30	Low back pain	Significant improvements in active vs control group for: 1) worse pain and pain interference states; 2) pain sensitivity measures, and 3) differential mRNA expression of 17 pain genes	Prospective, double-blind, placebo-controlled trial	

Appendix I

Algorithm 1: Basic Scrambler Treatment Algorithm



Algorithm 2: Advanced Scrambler Treatment Algorithm
(If patient does not meet criteria for proper electrode placement)

Option 1: Reduce Area of Pain

Place all electrodes above area of pain

- For feet, place electrodes on leg above area of pain, most likely minimum of 2 electrode sets, but may use as many as fit and are tolerated, or pain/tingling is zeroed
- For hands, place electrodes on arm above area of pain, most likely minimum of 2 electrode sets, but may use as many as fit and are tolerated, or pain/tingling is zeroed

Goal: Replace pain or tingling with new/different tingling sensation in the area of pain, in order to reduce area of pain/tingling and allow for proper placement of electrodes in next session

Treat for 30 minutes after tingling begins

* Patient assessed daily for ability to follow Algorithm 1

Option 2: Treat in area of pain

When electrode cannot be placed in area of non-pain, an electrode can be placed in the area of **least** pain and then Algorithm 1 can be followed

However, this can cause increased pain and discomfort and therefore this technique should be used based on provider experience and patient tolerability