A Pilot Study to Investigate the Benefits of a Cannabidiolic Acid Topical Cream for the Treatment of Restless Leg Syndrome

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Synopsis:

Restless Leg Syndrome (RLS) is multifactorial disease state with many different potential pathophysiological mechanisms, which includes dysfunctions from the cerebral cortex and spinal cord to mechanosensitive channels at the musculoskeletal periphery.[1] Most therapeutic agents' effectiveness focuses on the CNS (e.g., dopaminergic drugs) or Renshaw cells. To our knowledge, therapeutic agents that are focused on the periphery were not very effective.

This technology focuses on the peripheral musculoskeletal component of the disease and is directed at treatment modalities that correct the dysfunction of mechanosensitive channels. By combining what is known about cannabinoids activity at the transient receptor potential channel of ankyrin 1 (TRPA1)[2] and the role TRPA1 plays in regulating the shape and rigidity of the surrounding membrane structure at the Piezo channels[3], an effective therapy at the site of discomfort should emerge. Moreover, the lessening of membrane tension is imparted by molecules that readily penetrate the membrane[4], which Chylobinoid, the topical active ingredient, is uniquely designed to do.

If successful, we will demonstrate, for the first time, an effective treatment for RLS with a topically applied medicine. This medicine will virtually eliminate the safety concerns associated with current RLS treatments. Moreover, to our knowledge, this potential medicine will represent the first time that mechanosensitive channels will be the target of a cannabinoid to treat a specific disease state.

Abstract:

Anecdotally, we have preliminary observed 4-5 individuals with moderate to severe RLS describing near complete resolution of sensorimotor symptoms after consistently topically applying Chylobinoid™ cream to the affected extremities. We endeavor to validate these non-clinical observations by setting up a clinical trial with appropriate statistical power to demonstrate Chylobinoid's effectiveness of improving symptoms associated with RLS relative to placebo.

Our clinical endpoints will be measured using the International Restless Legs Syndrome Rating Scale

1. Statistically significant improvement of symptoms
2. A Minimally Clinically Important Difference of 3-point reduction.[5]

We will present the data at selected scientific meetings and, depending on the results, will publish the study in a peer-reviewed journal.

Significance:

This technology focuses on the peripheral musculoskeletal component of the Restless Leg Syndrome (RLS), a poorly understood sensorimotor disorder, and is directed at treatment modalities that correct the dysfunction of mechanosensitive channels that contribute to RLS's presumed mechanism of action. Our hypothesis is that modulating activity of the Piezo channels and acting on the TRPA1 that regulate the Piezo channels are key target areas to treat the symptomology of RLS.

Thus, an effective therapeutic agent to treat RLS targeted to the musculoskeletal periphery would be one that possesses three key properties:

1. Is amphiphilic enough to effectively penetrate, and consequently modulate, Piezo channel associated membranes.
2. Is known to modulate TRPA1.[2]
3. Can introduce divalent cations to interfere with the increased calcium flux initiated by overstimulation of Piezo channels.

Chylobinoid is a magnesium infused cannabidiolic acid (CBDa)-rich micellar complex derived from hemp extract.[6] The magnesium CBDa complex is polarity adaptive and that, combined with its micellar structure, imparts the measure of amphiphilicity desired for both relief of membrane tension with distortion of membrane structure and deep penetration through the epidermis to the target site. CBDa is also a potent TRPA1 ligand.[2] Finally, introducing magnesium into the system will contribute to disrupting the calcium flux.

We have already demonstrated, anecdotally, the effectiveness of topically applied Chylobinoid in improving the symptoms associated with RLS. The work described in this protocol is to prove Chylobinoid's effectiveness in treating RLS in a clinical setting.

Research Methods

Study design: Prospective open-label proof-of-concept trial.

Study Population: Subjects must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the Investigator and are subject to review in the event of a Good Clinical Practice audit and/or health regulatory authority inspection.

Inclusion criteria:

- Patients with at least 3 month-course of symptomatic restless leg syndrome
- Must meet International Restless Legs Syndrome Study Group (IRLSSG) criteria of at least mild symptoms.
- Age > 18 years, including both males and females
- Patient provides informed consent

Exclusion criteria:

- Previous operative procedure for treatment of RLS;
- Current use of TENS (transcutaneous electrical nerve stimulation or plasma exchange;
- Allergy to Cannabidiol (CBD) Cannabidiolic acid (CBDa), or any other ingredient contained in the topical cream;
- Pregnant participants (participants who have the potential for being pregnant will sign a waiver), or breast feeding;
- History of recreational substance abuse, fibromyalgia, Chronic Regional Pain Syndrome (CRPS), psychiatric history including but not limited to schizoaffective disorder, bipolar disorder, chronic depression, and suicidal ideation;
- Conditions affecting capacity and adherence to study regimen including but not limited to dementia/delirium, Alzheimer's, Down's syndrome;
- A need for elective surgery involving preoperative or postoperative analgesics or anesthetics during the study period;
- No recent cannabinoid use in the last 2 months, and no use during the study.

Participants and protocols:
Participants of both genders will be recruited. Participants with at least a three-month diagnosis of RLS without prior operative intervention will be approached for enrollment in the study. Participants will be enrolled once the trial is described, questions answered, and consent form signed. Pre-treatment IRLSSG scores are collected over the phone on new participant questionnaires. Anyone who does not meet the IRLS criteria for at least mild RLS with a minimum IRLS score of 7 will screen fail. Participants will then have the trial cream described, how to apply it (see below), and then the cream will be mailed to them. Once received, participants will use the cream at least once a night to the affected area(s).

The topical cream will be contained in a jar. The cream will be applied by hand from a measuring spoon and massaged into the skin. The participant will measure 1 teaspoon and apply this amount to each of the regions of the area the participant reports having RLS. Participants will be instructed to apply the topical cream once per day 30-45 minutes before bed for a total duration of two weeks. Participants will be instructed to re-apply the cream if they wake up and feel RLS symptoms.
Participants will receive a follow up phone call at the end of the 2-week study. Post-treatment IRLSSG and the PGIC (patient's global impression of change) will be collected at that time. That completes the study.

Sample Size: 10 participants

Primary outcome measure:

1.Statistically significant response to treatment using IRLSSG
2.A MCID of 3 using the IRLSSG

Secondary outcome measures:

1. Patients Global Impression of Change (PGIC)

Adverse Events
As this is a topical application of cream that is not expected to get systemically absorbed, the chance of an adverse reaction is small. The participants will be instructed to perform a skin patch test prior to beginning the study. If there is any skin irritation, rash, itch or welts, the participant is instructed to wash the area with lukewarm water and soap and if needed apply Vaseline petroleum jelly or Aquaphor or its generics for comfort and to call the PI. If this occurs, the participant will not continue with the study.

Compensation: Participants will receive the trial cream free of charge**.**

Statistical Analysis Plan:

The baseline and post-intervention observations of the IRLSSG will be calculated using the associated scoring rubric. The distribution of baseline scores will be subtracted from the distribution of post-intervention observations to yield a distribution of difference scores. A Shapiro-Wilk test will be performed on the distribution of difference scores to assess normality. If the assumption of normality is met, parametric paired-samples t-test will be performed to test for significant change in IRLSSG scores. Means and standard deviations will be reported and interpreted for the t-test analysis. If the assumption is violated, then a non-parametric Wilcoxon Signed Rank test will be performed to test for change in IRLSSG scores across time. Medians and interquartile ranges will be reported for the non-parametric test. The PGIC will be scored using its associated scoring rubric. Normality of the two questions from the PGIC will also be tested for using Shapiro-Wilk tests. If the distributions for the questions are normal, means and standard deviations will be reported, and if either or both distributions are non-normal, then medians and interquartile ranges will be reported. All analyses will be conducted using SPSS Version 29 (Armonk, NY: IBM Corp.) and statistical significance will be assumed at an alpha value of 0.05.

References

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2. De Petrocellis, L., et al. “Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8.” The Journal of pharmacology and experimental therapeutics, 325,3 (2008): 1007-15.
3. Moparthi, L., Zygmunt, P. M.; “Human TRPA1 is an inherently mechanosensitive bilayer-gated ion channel”, Cell Calcium, Volume 91 (2020): 102255.
4. Fang, XZ., Zhou, T., Xu, JQ., et al. « Structure, kinetic properties and biological function of mechanosensitive Piezo channels”. Cell Biosci 11, 13 (2021).

5. Allen RP. Minimal clinically significant change for the International Restless Legs Syndrome Study Group rating scale in clinical trials is a score of 3. Sleep Med. 2013 Nov;14(11):1229
6. Piccariello, T., Palmer, S., Mulhare, M.; “Solid Micellar Compositions of Cannabinoid Acids”; International Application No. PCT/US2020/014109, filed January 17, 2020

List of Abbreviations

RLS, Restless Leg Syndrome; TRPA, transient receptor potential channel of ankyrin; CBDa, Cannabidiolic Acid