Restless Leg Syndrome Treatment with Topically Applied Chylobinoid

Summary of the Medical Technology

This medical technology expounds upon the original Solid Micellar Composition of Cannabinoid Acids technology, which is patent pending (Application Number 17/423,846). The technology disclosed therein described a composition of magnesium infused CBDa-rich micellar complexes of hemp extract, which is collectively termed chylobinoid™. Recently, it was discovered that chylobinoid is effective in the treatment of Restless Leg Syndrome (RLS). Herein is the description of the new application.

Importance of Mechanosensitive Channels

RLS is a relatively common neurological sleep disorder affecting up to 15% of the general population. It's a multifactorial disease with many potential pathophysiological mechanisms including abnormal excitability of the cerebral cortex and spinal cord and of mechanosensitive channels at the musculoskeletal periphery.[1] Therapeutic agents usually used target the central nervous system (dopaminergic drugs), neurotransmitter pathways (GABA analogs like gabapentin, pregabalin, valproic acid), and adenosine (e.g. dipyridamole) in an attempt to improve symptoms. Additionally, supplementation with iron, Vitamin B1 (thiamine) and magnesium may have mild ameliorating effects. However, there are virtually no effective therapeutic agents that are focused on the peripheral pathological expression of this disorder.

Hypothetically, treatment of RLS can alternatively focus on the peripheral musculoskeletal derangements thought to be associated with the disease. More specifically, aberrant mechanosensitive channels that mediate abnormal sensorimotor information flow. This medical technology is intended to improve irregular Piezo channel signaling through interaction with associated TRPA1 receptors and thus become a novel therapeutic approach to improve the disagreeable symptoms that define the disease.

This may be accomplished in three biologically linked ways. The first is potentially modulating the membranes surrounding Piezo channels. Various modulators such as pH, temperature, divalent ion concentrations, alternative splicing, osmotic swelling, membrane lipid composition, co-expression of other membrane proteins, and G-protein-coupled pathways have been reported to regulate the Piezo channel kinetics.[2] By focusing on the nature of the divalent ion and membrane integrity, Piezo channel gating can be properly controlled. Piezo channels are regulated by the shape and rigidity of the surrounding membrane structure. Membrane tension is lessened with distortion of membrane structure, which is imparted by molecules that readily penetrate the membrane, such as amphiphilic molecules.[2] Indeed, it was found that the snake venom peptide, GsMTx4, inhibits the Piezo1 channel, not by binding Piezo1 directly, but rather acting via modulating local membrane tension near the channel.[3]

Human TRPA1 (hTRPA1) is an inherent mechanosensitive channel that like the other mammalian mechanosensitive channels TREK-1, TREK-2, TRAAK and Piezo is gated by force-from-lipids (FFL).

Lipophilic compounds also act on TRPA1 by membrane bilayer perturbation, which impacts force amplification of Piezo channel response to mechanical stimulation.[4] Therefore, it is amphiphilicity, as in GsMTx-4, and not lipophilicity that drives the membrane bilayer perturbation.

hTRPA1 is also involved in the MOA of RLS through oxidative stress, which can shape the response to mechanical stimuli by shifting hTRPA1 into a force-to-lipid sensitive protein conformation. Moreover, the effect of non-electrophilic TRPA1 ligands may be indirect by changing the lipid tension stress on TRPA1 within the cell membrane. [5]

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.
3. Can introduce divalent cations to interfere with the increased calcium flux initiated by overstimulation of Piezo channels.

Pharmacodynamic Importance of CBDa

Many of the benefits attributed to cannabinoids stem from the effects that cannabidiol (CBD), and its acid form cannabidiolic acid (CBDa), have on key receptors and enzymes. While their mechanisms of action remain under study, the data strongly suggest that these cannabinoids act on multiple central nervous system receptors (e.g., serotonin), ion channels (e.g., vanilloid, TRPA1) and enzymes (e.g., COX-2). Most relevant is the potent and efficacious modulatory effects by some phytocannabinoids, namely THC, CBD, CBC, CBG, THCa and CBDa, on TRPA1.[6]

CBDa was shown to be as high as 100 times more potent than CBD in treating pain due to inflammation.[7] This is explained, in part, because CBDa is not only 9 times more potent than CBD at inhibiting COX-2, but it is also more selective at inhibiting COX-2 versus COX-1.[8] Primarily, COX-2 induces inflammation while COX-1 maintains the normal lining of the stomach. This explains why when taking non-selective NSAIDs (non-steroidal anti-inflammatory drugs), some patients experience gastric distress and reflux symptoms because of off-target inhibition of the COX1 enzyme. In addition, CBDa is more potent at receptor sites PPARγ which also regulate pain and inflammation[9], and CBDa is generally more effective in the treatment of inflammation associated with microbial infections, sun-related skin reactions and eczema.[10]

CBDa is the predominant cannabinoid produced by many cannabis strains and demonstrates the importance of the interplay between cannabinoids and cannabinoid receptors. For example,

during their research with the health-critical serotonin receptor Bolognini[15], et. al., concluded that "compared with cannabidiol, CBDa may display greater potency, efficacy and selectivity at ameliorating signs of cerebral infarction, anxiety and depression via (serotonin) receptor-dependent mechanisms in animal models." This is a very important component of CBDa's health benefits because the serotonin receptors broadly influence various biological and neurological processes such as aggression, anxiety, appetite, cognition, learning, memory, mood, nausea, sleep, and thermoregulation.

Cannabinoid benefits can also be attributed to the recent discovery of the endocannabinoid receptors throughout the central nervous system.[16] This deeply integrated endocannabinoid system (ECS) has helped us recognize and understand many of the health benefits of cannabinoids. This is explained, in part, by the cannabinoid molecules' variable affinity for cannabinoid receptors expressed throughout the human body (although recently discovered, cannabinoid receptors are even expressed in very rudimentary species of animals). Both CBD and CBDa stimulate the ECS indirectly and do so in different ways. That is why it is important to have both CBDa and CBD in your cannabinoid product, like what is found in Chylobinoid, to optimize this recognized "entourage effect".

Chylobinoid consists of approximately 70% CBDa, 5% CBD, 5% other cannabinoids, 4% magnesium and other naturally occurring plant lipids.[11] Chylobinoid delivers the benefits of CBDa and offers these advantages:

- **It has better bioavailability** than CBD because Chylobinoid generally bypasses the liver and is more directly absorbed into the bloodstream. Most conventional CBD products taken orally are filtered down to approximately 8% of their potency due to the combination of poor oral solubility and significant first-pass hepatic metabolism.[12]
- Has **deeper skin penetration** because the magnesium coordination with the CBDa creates a polarity adaptive molecule which is both water and fat miscible and allows the compound to penetrate through the dermis and epidermis to reach pain receptors more effectively.[13,14]

In addition to relief from RLS, the health benefits that are derived from chylobinoid also potentially include:

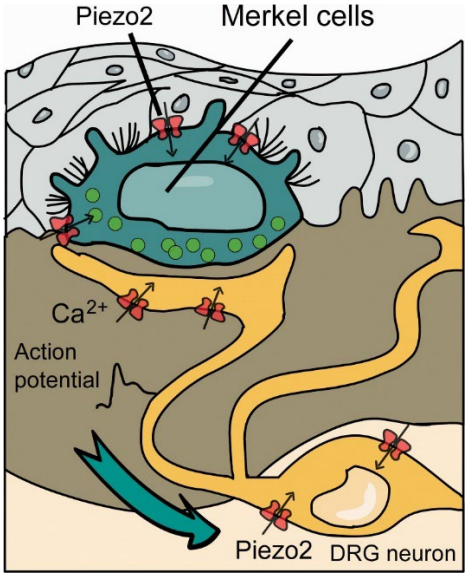
- Pain and inflammation relief
  Reduced anxiety and stress
- Improved sleep
- Potential suppression of any concurrent seizure activity
- Improved control of migraine headache pain

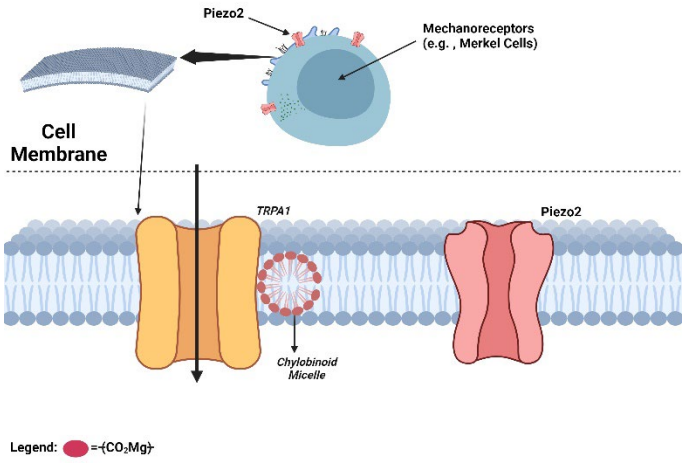
All of these possible health benefits may contribute, indirectly, at least, to the efficacy chylobinoid has in ameliorating and managing the symptoms associated with RLS.

Pharmacokinetic Importance of Chylobinoid

Topical medicaments applied to skin need to penetrate through the epidermis into the dermis and then permeate targeted areas (e.g., Piezo channels) in quantities sufficient to exert a therapeutic effect. The epidermis, with its tightly packed keratin, serves as a barrier to prevent incidental molecules from randomly penetrating the dermis. Properly formulated molecules, however, can penetrate the epidermis. In general, the deeper into the dermis analgesic molecules penetrate, the more channels, nociceptors and receptors are affected. Sometimes the compounds can reach the micro-vasculature (tiny blood vessels in the dermis), which allows the compound to reach even deeper tissue. With advanced formulations, the therapeutic effect may even reach synovia (the soft tissue surrounding joints, tendon sheaths, and bursae), where even more secretory cells (e.g., Merkel), nerve fibers and Piezo channels reside.

Chylobinoid is primarily a magnesium coordinated CBDa complex[11] and, therefore, is designed to impart its therapeutic effects deeper into the dermis (through the epidermis) and deeper soft tissues where Piezo channels are located. Chylobinoid's Piezo channel calming effects are maximized because of the relatively dense expression of Merkel cells, Piezo channels and microvasculature within the dermis. In general, the epidermis can be viewed as consisting of multiple layers of water repellant membranes and biological partitions. With this medical technology, a mineral coordinated complex like Chylobinoid can switch from being water soluble to membrane penetrating and, therefore, have a unique ability to adapt so that penetration through the epidermis and dispersion into deeper dermis layers is facilitated.





Clinical Trial Design

A pilot study to investigate the benefits of a cannabidiolic acid topical cream for the treatment of restless leg syndrome was initiated. We enrolled 10 adults with a diagnosis of restless leg syndrome who have suffered with symptoms for over six months and scored a 7 or greater on the International Restless Leg Scale (IRLS). This was an open label study and the participants who were on medications for the treatment of restless legs, with the exception of cannabinoids, were permitted to continue those medications. Participants were instructed to use the cream on the affected area 30-45 minutes prior to bedtime for two consecutive weeks. Participants were surveyed after two weeks of treatment using the IRLS scale and the Patient's Global Impression of Change questionnaire (PGIC). Every participant but two had a statistically and clinically significant improvement of their restless legs and none reported any adverse effects. This is a significant improvement over current systemic pharmaceutical treatment options that have a poor track record for treatment success and/or have many adverse effects.

Statistical Analysis

Table 1.

PGIC Questions

PGIC Question	*Mdn* (IQR)
Question 1	6.50 (5.00 – 7.00)
Question 2	0.00 (0.00 – 1.00)

Note: *Mdn* (IQR) – Median (interqurtile range)

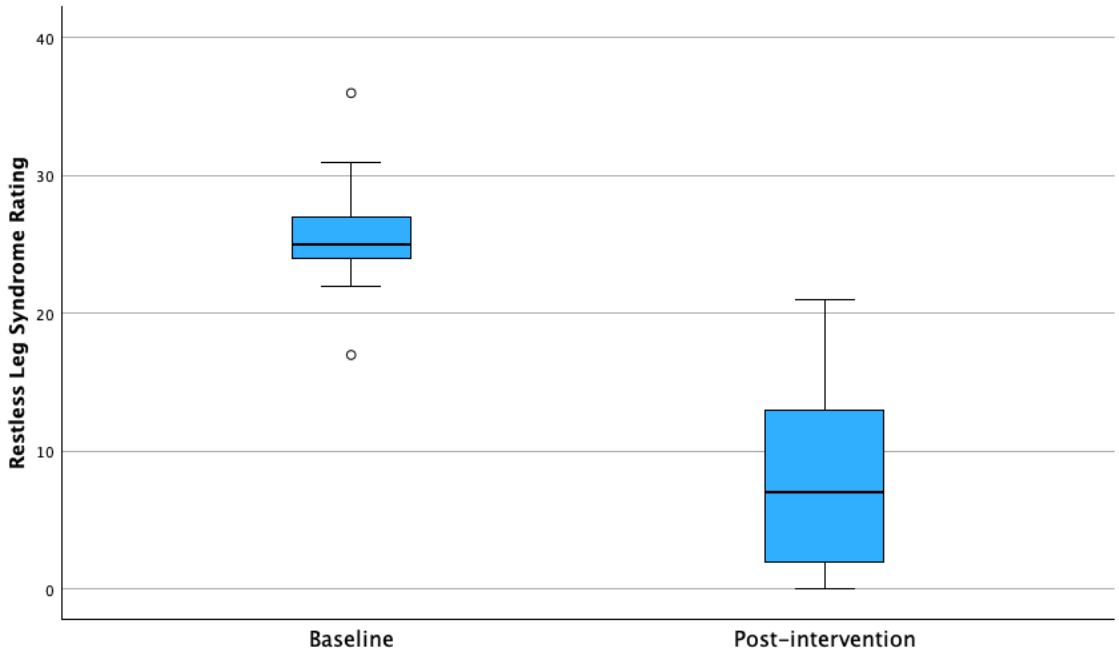
Table 2.

Repeated-Measures *t*-tests

Outcome	Baseline (*M*, SD)	Post-intervention (*M*, SD)	Mean difference (95% CI)	*p*-value
IRLS	25.80 (5.05)	8.00 (7.27)	17.80 (11.68 – 23.92)	< 0.001
RLS Ordinal Scale	5.20 (1.87)	1.40 (1.65)	3.80 (2.34 – 5.26)	< 0.001

Figure 1.

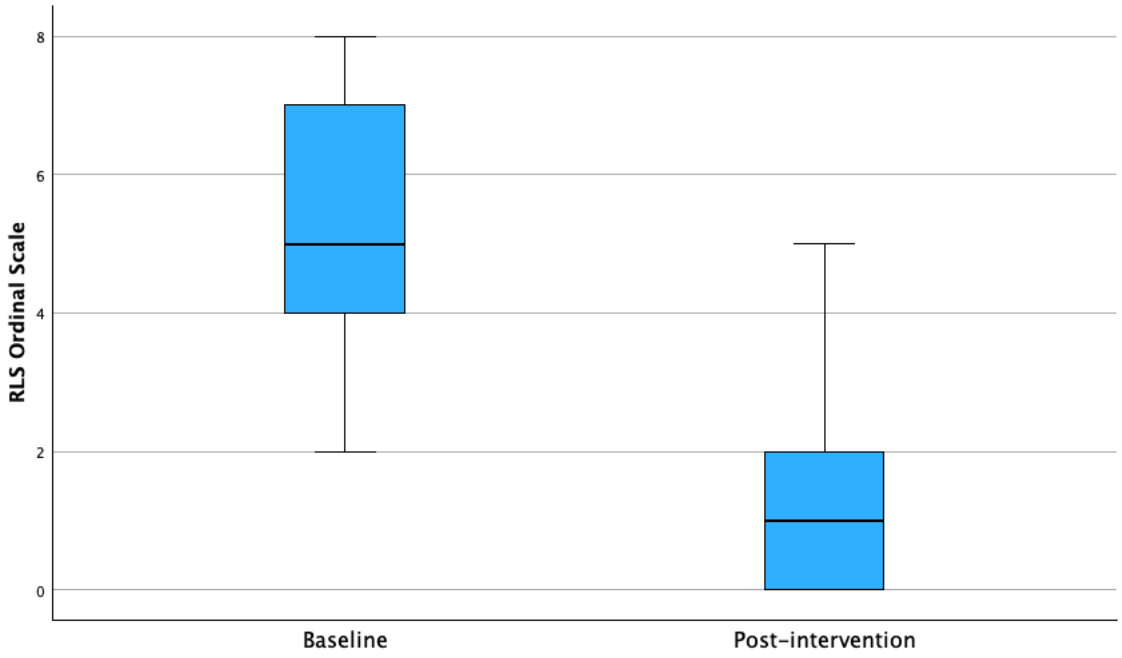
IRLS Across Time



Note: Small circles denote outliers at 1.5X the interquartile range

Figure 2.

RLS Ordinal Scale Across Time



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