WHITEPAPER

Relegs®

A non-pharmacological treatment option for RLS

THE POPULAR PRODUCT FOR PEOPLE WITH RLS

Preface

We believe we can make a major impact on the daily wellbeing of people suffering from the restless legs syndrome (RLS) through counterstimulation with electrical pulses. That is why we designed Relegs®, a miniature wireless device that helps people to reduce their symptoms in every RLS situation, to sleep better and to regain quality of life.

Our mission is to improve and expand the therapeutic repertoire for RLS with innovative non-pharmacological treatment solutions. Therefore, we strive for Relegs® to be included in the NHG* standards as first treatment option for moderate RLS and as adjunctive to pharmacotherapy. The objective of this whitepaper is to provide:

a) The argumentation for the need for non-pharmacological treatment solutions for RLS;
b) The scientific basis for the treatment of RLS with Relegs®.

*Evidence-based guidelines in Dutch healthcare system

INTRODUCTION

RLS is generally a lifelong condition, the exact cause remains unknown, there is no cure and treatment is directed at symptom relief only. Pharmacotherapy dominates the treatment strategy, but due to the limited effect and related side effects, like tolerance, addiction and augmentation, it is only considered when patients suffer from severe RLS and recommended for only a relatively short period of time (6-24 months) [1]. Complementary and alternative therapies, like exercise training and lifestyle changes, (pneumatic) compression therapy, infrared therapy, vibration therapy, transcutaneous spinal direct current stimulation, and acupuncture have been found effective in reducing RLS symptoms, but scientific evidence is scarse [2-6].
There are no medical devices on the market intended to treat RLS, other than a foot wrap that produces pressure on targeted foot muscles [7]. This device is not practical to use in every situation that RLS symptoms occur. There is a need for more and better treatment solutions to improve the therapeutic repertoire for RLS.

ABOUT RLS

RLS "The most common unknown disease"

The prevalence of RLS in general population ranges from 5% to 10%. In approximately 2-3% symptoms are clinical significant, so that treatment is required [8,9]. With the EU population estimated at 450 million, the number of people in the EU with RLS ranges from 22,5 to 45 million, and those with clinical significant RLS 9 to 13,5 million.
An epidemiological study (2121 patients) into the prevalence and impact of RLS in Dutch general practice found a prevalence of diagnosed RLS of 6%, of which 23.6% had moderate to severe symptoms.
Most of the patients (84%) did not recognize themselves as RLS patient [10]. A population-based survey in Germany with 1312 participants found a prevalence of RLS with a known doctor diagnosis in 2,3% and in 6,5% patient fulfilled the RLS criteria, but did not know about the diagnosis. 33.3% of the patients with a known RLS diagnosis had a wish for treatment. In patients with an unknown diagnosis, there was a wish for treatment in 14.1% of cases. [11].

Definition of RLS

The International Restless Legs Syndrome Study Group (IRLSSG) defines RLS as follows:

"Restless legs syndrome (RLS), a neurological sensorimotor disease often profoundly disturbing sleep and quality of life has variable expression influenced by genetic, environmental and medical factors. The symptoms vary considerably in frequency from less than once a month or year to daily and severity from mildly annoying to disabling. Symptoms may also remit for various periods of time. RLS is diagnosed by ascertaining symptom patterns that meet the following five essential criteria"

1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
5. The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

Quality of Life

People suffering from RLS will avoid places and events where they have to be inactive for a longer period of time, e.g., cinema, theatre and meetings. RLS also makes traveling difficult. Many people with RLS report they are often unable to concentrate, have impaired memory, or fail to accomplish daily tasks. Untreated moderate to severe RLS can lead to about a 20 percent decrease in work productivity and can contribute to depression and anxiety. Eventually, RLS can cause exhaustion and daytime sleepiness, which can strongly affect mood, concentration, job performance, and personal relationships [12].
RLS has a significant negative effect on sleep and quality of life [9, 10].

RLS "a burden on healthcare budgets in Europe"

A report from the European Brain Council reveals poor diagnosis and treatment of RLS which makes it one of the most costly neurological disorders in Europe. The total cost of poor diagnosis and treatment of RLS in Germany, Italy and France is significantly higher than the combined cost of Parkinson's disease, Multiple Sclerosis and Epilepsy in these countries, partially due to high prevalence of RLS [13].
The health economic burden of patients with RLS in Germany has been estimated [14]. The average total costs over a 3-month observation period were calculated €2090,-. The average direct medical and non-medical costs from the perspective of the health insurance provider were determined to be €780, with €300,- attributed to medication costs and €354,- to hospitalization costs. The average total indirect costs amounted to €1308,- and were calculated based on productivity loss, using the human capital approach.
The socio economic burden of RLS has been estimated for the EU by analyzing three separate healthcare systems (Germany, France, Italy) [15]. Pooled data from the three countries showed that RLS economic impact

varies between €20,188.68 million per year, when the prevalence of RLS patients wishing for treatment is assumed to be 1.6% of the population [11], to €34,068.41 million per year, when the prevalence of RLS patients is assumed to be 2.7% of the population [9] for the three EU countries (France, Germany, and Italy) combined. The estimates included health care costs as well as indirect costs to society, such as lost productivity due to reduced ability to work or to work at full capacity.

RLS and Placebo

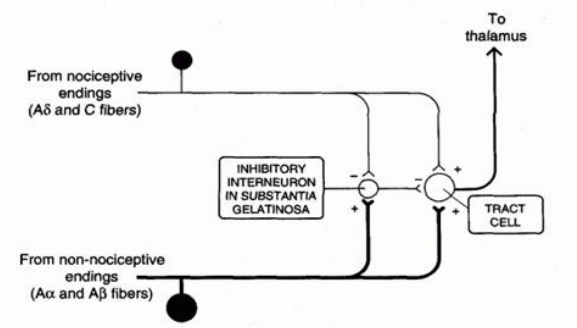
RLS is unique in the sense that it responds to both dopaminergic and opioidergic agents and it is thought that the dopamine and opioid systems play a crucial role in the physiological response to a placebo. A meta-analysis to quantify the magnitude of the placebo effect in RLS pharmacological treatment studies revealed a substantial pooled placebo response rate of 40% and on average more than one-third of RLS patients experienced a major improvement of RLS symptoms while being treated with a placebo [16].

The standards for the Dutch General practitioners consider treatment with dopamine agonists, when patients suffer from severe symptoms, despite limited effect and high placebo (>50% symptom improvement in 60% of patients versus 40% of placebo users) and high rate of possible side effects [1].

RLS and pain

RLS was originally described in 1945 by Karl Ekbom, who reported two forms of the syndrome: one characterized by dysesthesias, ‘asthenia crurum paresthetica’ and one by pain, ‘asthenia crurum dolorosa’ [17]. Broadly, pain is defined as any unpleasant sensation with a negative affective component. Traditional pain symptoms occur in about 20% of RLS patients, but depending on semantics on how pain is defined 80%

may report some pain [18,19]. Thus, although the majority of RLS sufferers specifically state that the sensation is not “painful”, approaching RLS from this point of view offers the potential to offer novel non-pharmacological treatment strategies.



Simple illustration of the gate control theory of pain. Non- nociceptive sensory fibers stimulate the inhibitory interneurons, whereas nociceptive afferents inhibit them. An increase in non-nociceptive input will reduce the rate of firing of the spinothalamic tract neurons.

Theoretical foundation for working principle Relegs®

Gate Control Theory

The gate control theory is developed by Melzack and Wall in 1965 [20] and re-examined by Wall [21] in 1978. It proposes that a metaphorical gate, consisting of excitatory and inhibitory synapses, exists in the dorsal horn of the spinal cord. This gate regulates the amount of painful stimuli being transmitted onwards to the brain; it opens by noxious stimuli that excites high threshold small diameter peripheral afferents and can be closed by non-noxious stimuli (e.g. touch, pressure, vibration and electrical stimulation) that excites low threshold large diameter peripheral afferents. We experience this phenomenon in daily life when rubbing the spot where an injury has just occurred. RLS patients seek relief by resorting to overwhelming tactile stimulation, like moving, rubbing, massaging, punching or squeezing the legs when unpleasant symptoms occur. The gate control theory is generally accepted and was revisited in 2016 with a neurocomputational model. The results are consistent with biological ones in that pain signals are blocked on their way to the brain every time a tactile stimulus is given at the same place where the pain was produced [22].

Spinal mechanism (segmental)

Electrical stimulation produces analgesia predominantly by a segmental mechanism whereby activity generated in Aβ fibres inhibits ongoing activity in second-order nociceptive neurons in the dorsal horn of the spinal cord. It has been shown that activity in large diameter afferents will inhibit nociceptive reflexes in animals when the influence of pain inhibitory pathways descending from the brain has been removed by spinal transection [23, 24]. Garrison and Foreman [25] showed that electrical nerve stimulation could significantly reduce ongoing nociceptor cell activity in the dorsal horn cell when it was applied to somatic receptive fields. Follow-up work after spinal cords had been transected at T12 demonstrated that spontaneously and noxiously evoked cell activities were still reduced during electrical stimulation. This demonstrates that the neuronal circuitry for electrical nerve stimulation analgesia is located in the spinal cord and it is likely that a combination of pre- and postsynaptic inhibition takes place [26]. The clinical observation that electrical nerve stimulation produces analgesia that is short lasting and rapid in onset is consistent with synaptic inhibition at a segmental level.

Peripheral mechanism

The delivery of electrical generated signals over a nerve fiber will elicit nerve impulses that travel in both directions along the nerve axon, termed antidromic activation. Electrical generated nerve impulses travelling away from the central nervous system will collide with and extinguish afferent impulses arising from tissue damage. Antidromic activation is likely to occur in large diameter fibers and as tissue damage may produce some activity in large diameter fibers the induced signals may mediate some of its analgesia by peripheral blockade in large diameter fibres. Transcutaneous electrical signal blockade of peripheral nerve transmission has been demonstrated by Walsh et al. [27] in healthy human subjects.

Practical foundation for working principle Relegs®

Transcutaneous electrical nerve stimulation (TENS) is a well-established treatment modality used for chronic pain and other pain conditions, of which some are associated with RLS, including migraine [28], fibromyalgia [29], multi-site pain [30] musculoskeletal pain [31], and peripheral neuropathy [32,33].

Electrical nerve stimulation also has been found successful in a patient with RLS-like symptoms [34]. Furthermore, it is suggested that pre-sleep neuromuscular stimulation of foot and toe dorsiflexors represents a promising treatment of PLMS with or without RLS [35]. The results of a pilot study with transcutaneous spinal direct current stimulation have demonstrated a clinical improvement in RLS and support the pathophysiological concept of spinal cord hyperexcitability in idiopathic RLS [36]. A randomized crossover study evaluating the effect of external sensory stimulation on RLS found a tendency towards less leg discomfort [37]. Finally, TENS has been found successful in the treatment of restless legs in combination with Restless genital syndrome [38].

NON-PHARMACOLOGICAL SOLUTION

The International Association for the Study of Pain (IASP) describes conventional TENS as “High-frequency (50-100 Hz), low-intensity (paraesthesia, not painful), small pulse width (50-200 µs)” with the intention to stimulate selectively large diameter, low threshold non-noxious afferents (Aβ) in dermatomes related to the pain.
This inhibits activity in second order nociceptive transmission neurones in the central nervous system and is achieved by increasing TENS pulse amplitude to generate a strong, comfortable, non-painful paraesthesia beneath the electrodes [39].

Relegs® a new non-pharmacological solution for RLS

Relegs® is an innovative, CE certified (medical class IIA), conventional TENS device intended to use for the treatment of RLS. It has an ergonomic design that specifically takes into account the different RLS postures and situations and includes space technology for high safety and reliability electronic design. Relegs® is a non-pharmacological solution to relieve RLS symptoms in every RLS triggering posture and situation, including travelling and in public domain. Relegs® has a unique patented peel-off detection system for a safe night use.
Relegs® can be used as standalone treatment and as adjunct to pharmacotherapy. With Relegs, patients may reduce the amount of medication they need to control their symptoms.
Relegs® may be beneficial for RLS sufferers, in case:

- Moderate to moderate-severe RLS (and pharmacotherapy is not considered);
- As adjunct to pharmacotherapy (when medication alone is not effective);
- Pharmacotherapy is not desired (e.g., due to side effects).

The Relegs® treatment has been derived from the theories and studies discussed above and has been further finetuned (pulse signal pattern with mixed frequencies) by testing at Relegs and validated by the clinical data as discussed below. The intensity is found critically important to

obtain a positive effect; a strong but comfortable intensity provides a significant analgesic effect, whereas electrical stimulation delivered below sensory threshold is found ineffective. Relegs advises to increase intensity to a strong but comfortable sensation, just below pain threshold.

Clinical data Relegs®

A prospective interventional study has been conducted with a clinical prototype of Relegs® to assess its efficacy for RLS treatment. Difference in RLS Visual Analog Scale (VAS) scores were analyzed before and after treatment with the clinical prototype. Mixed model analysis was used to correct for the dependency of measures within patients. This study was approved by the Medical Ethical Committee-LDD and was performed at Centrum Oosterwal, outdoor clinic for dermatology & phlebology.
In twelve RLS patients (range 46-71 yrs) with moderate to severe RLS (IRLSS range 11-26) a total of 134 RLS attacks were recorded with VAS. After exclusion of 8 RLS attacks, due to malfunction of the prototype, the mean difference in VAS scores (before score – after score) for the total population was 40 mm (95% CI 24-55, $p<0.001$). In 67% (8 out of 12 patients) a mean reduction in VAS of 30 mm or more was found.
It is reported that a mean reduction in VAS of 30 mm represents a clinically important difference in pain severity that corresponds to patients' perception of adequate analgesic control [40]. This confirms the clinical performance and intended purpose of Relegs®. Though, the study design was susceptible to placebo effects. A placebo-controlled trial is planned as part of post market clinical follow-up. Relegs® is on the Dutch market with a money-back guarantee if user is not satisfied.
After one year of sales in the Netherlands, 65% of the users is satisfied with the treatment results of Relegs®.

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Relegs® relieves your RLS, wherever you are.

Relegs®