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Preamble

Chronic pain is a global problem with prevalence in Europe estimated at 19%[1] and up to 30,7% in the USA[2]. These numbers, which keep growing as the population ages, have a significant economic impact due firstly to a decreased productivity for people of working age, and secondly to the cost of medical care. Chronic pain also has a profound impact on people's lifestyle and quality of life, half of chronic pain sufferers being constantly in pain and a third considering their pain to be severe. A study conducted in the US[1] reports 61% patients being less able or unable to work outside the home, 19% having lost their job due to their condition, 3% having changed jobs because of their pain and 21% having been diagnosed with depression because of their pain.

Opioid analgesics are very useful for acute pain and pain at the end of life. They completely change the experience of patients enduring severe pain, especially post-surgical pains and they should keep being used for the relief of moderate to severe pains. However, in the United States, pharmaceutical companies' unfounded claim in the late 1990s that patients would not become addicted to opioids led to an explosion in both prescription and misuse of opioids, now known as the "opioid overdose crisis". This crisis multiplied the number of deaths by opioid overdose by a factor of 5.9 between 1999 and 2017, with 47,770 deaths due to opioid overdose in 2017 in the US (USA National Institute on Drug Abuse). Patients receive a large quantity of opioids for too long post-surgery, leading them to use opioids long after the original prescription, and to stockpile them for their own later use or that of their family members.

The impact of this crisis is such that it is a major factor in the decline of life expectancy in the US over the past few years[3]. This is just one of many red flags signaling the urgent need to find better methods for the management of chronic pain. In this search, solutions that rely on the body's own pain modulation system show a great deal of potential. The body possesses its own opioid system, using molecules with more potent analgesic effects than morphine. Because the release of endogenous opioids is triggered by the stimulation of the peripheral nervous system, treatments such as massages, thermal cures, acupuncture, and cryotherapy are often proposed to patients. These solutions, though effective, require significant expenditure of time, money and efforts. The first non-drug treatment recommended to patients with chronic pain is "physical exercise", but it is extremely difficult for sufferers to take physical exercise when even simple everyday gestures are painful.

Remedee Labs is developing a safe, convenient, self-managed solution that has the potential to relieve people not only from the burden of chronic pain, but also from conditions involving sleeplessness, stress, mood and reward regulation. The solution uses the emission of millimeter waves (MMW) that stimulate the peripheral nervous system, provoking the intracerebral release of endorphins (endogenous opioids). Here, we present a documented summary of endorphins and millimeter wave therapy justifying Remedee Labs' approach and the scope of the projects in development. In the first part of this document, we describe the nature, regulation, physiological mechanisms and effects of endorphins. In the second part, we describe MMW therapy from its discovering in the 1970s' in the Eastern-bloc countries to the development of our miniaturized solution, the Remedee One. We also summarize numerous clinical trials published in the literature showing the efficacy of MMW therapy in pain management. The third part describes the first clinical trial assessing the safety of our device and we finish with a description of our planned program of clinical trials to demonstrate our solution's efficacy.

1 Endorphins

1.1 Background

Endorphins are neuropeptides secreted by the body and acting as opioids. Their name come from the contraction between "endogenous", meaning "proceeding from inside" and "morphine", from "Morpheus", the Greek god of sleep and dreams. The analgesic and sedative properties of opioids have been known since Antiquity: opium was extracted from the poppy flower in Mesopotamia and used both for its medicinal and relaxing properties. They are currently considered as "natural pain-killers", "well-being hormones" or "feel-good chemicals".

The existence of the opioid system in the central nervous system was first evidenced by the identification of opioid receptors in the brain[4,5] and later of their endogenous ligands called Met- and Leu-enkephalin[6,7]. Since then, many other endogenous opioids have been identified, namely: enkephalin, dynorphin, and β-endorphins.

Endorphins are one kind of opioids derived from the precursor protein pro-opiomelanocortin[8] (POMC). They are produced continuously in various parts of the body, but especially in the nervous system and the pituitary gland and interact mainly with cell receptors of the nervous system responsible for blocking pain and its emotional processing. Their production varies dramatically both inter and intra individually, depending on factors such as people's age, activities, mood, or even the time of day.

After binding to specific receptors, endorphins are degraded by enzymes called enkephalinases after about an hour[9,10]. Despite this rapid degradation, biological effects of endorphins remain for a longer duration due to the triggering of a chain of second messengers leading to a global activation of the parasympathetic system.

1.2 Regulation: the involvement of peripheral stimulation

Increases in endorphin levels in situations applying heavy strain on bodily tissues, especially painful stimulation, physical exercise or childbirth, led to the hypothesis that intracerebral endorphin levels depend on peripheral nerve stimulations. Corroborating this idea, several triggers have been identified, amongst which we can mention:

Pain: At a clinical level in humans, several studies have highlighted a strong negative correlation between patients' blood endorphin concentration and their pain score[11]. Experiments on humans[12] and rats[13], show nociceptive stimuli lead to an increase of β-endorphin levels in blood plasma. Moreover, intracerebral injection of exogenous β-endorphins leads to an analgesic effect about 30 times stronger than that of morphine[14].

Physical exercise: Intense physical exercise leads to a rise in endorphin levels (for a review, see [15]). The strain exercised on muscles activates ergoreceptors, which send signals to the brain via afferent sensitive nerves. This provokes endorphin release both in the central nervous system and the blood stream[16].

Pregnancy: During pregnancy, endorphin levels increase after the first trimester to reach their maximal levels during birth. This increase is caused by the stretch of the uterus, which stimulates the pelvic nerves[17,18]. High endorphin levels during pregnancy are associated with a higher pain threshold[19,20].

Temperature: numerous worldwide stimulation technics use temperature variations (i.e. thermal stress) to induce an endorphin release, e.g. sauna[21], hot-spring baths[22], cryotherapy[23]. Transient Receptor Potential Vanilloid receptors (TRPV 1-4) are considered as the major cellular sensors for detecting increases in temperature. Their channel proteins convert changes in thermal energy into electrical activity conducted to the central nervous system. TRPV1 is activated by heat >43°C as well capsaicin, the pungent chemical present in chili peppers.

Capsaicin, like thermal stress, has analgesic properties meditated by an increased activity of the cerebral opioid system when it is administrated[24]. For this reason, capsaicin is used in patches to help with neuropathic pain management[25].

Cutaneous contact: The activation of cutaneous mechanoreceptors by connective tissue massage results in a moderate release of plasma β-endorphin that lasts for about an hour[26].

Light: In humans[27] and mice[28], exposure to UV rays lead to an increased production of endorphins. In mice, experimentally induced withdrawal signs were observed after chronic exposure to UV rays was stopped, confirming the hedonic role of β-endorphins that contribute to seasonal affective disorders during seasons with less light (i.e. autumn and winter)[28].

1.3 Physiological processes

1.3.1 At the cellular level: neurotransmission and hormonal function

Endorphins secreted in the central and peripheral nervous systems behave as neuromodulators. In the peripheral nervous system, endorphins bind to both pre- and post-

synaptic membrane receptors and reduce interneural signal transmission[29,30], especially that of substance P, a nociceptive neurotransmitter. In the central nervous system, endorphins are involved in the descending regulation of pain, by inhibiting the release of GABA, resulting in abundant release of dopamine[29].

Endorphins are also synthesized by the pituitary gland (which sits outside the blood-brain barrier), and are released into the circulatory system in the same way as hormones[31]. Endorphins released in this way circulate through the whole body and their action is similar to that of exogenous opioids (e.g. morphine) especially in nociception/analgesia[32,33] and euphoria.

1.3.2 At the systemic level: changes in the sympathetic/parasympathetic balance

Homeostasis is a dynamic equilibrium which keeps the body maximally functional in various situations. The autonomic nervous system is divided into two sub-systems with opposite effects on homeostasis. The functional interaction between the sympathetic and the parasympathetic nervous systems works to return the body to the required state of homeostasis. On one hand, the sympathetic nervous system regulates the adaptive response to stress - the so-called "fight-or-flight response"[34], preparing the body to react to threatening situations. On the other hand, the parasympathetic nervous system promotes "rest-and-digest" activities[35].

The role of endogenous opiates in interaction with the autonomous system has been exhaustively described in a review by Holaday[36]. As the author mentions, the dense population of opioid receptors in the hypothalamus, hypophysis, brainstem, and in proximity to cardiovascular centers is a strong indicator of the role of endogenous opioids in the balance between sympathetic and parasympathetic systems. Subsequent experiments have shown, for example, that intracerebroventricular injection of β-endorphins in rats suppresses sympathetic nerve activity in a dose-dependent way[37]. Endogenous opioids modulate the sympathetic system's action on the heart by inhibition of the β-adrenergic activity[38]. In dogs, mu- receptor agonists affect heart activity by increasing R-R intervals, as well as inducing hypoventilation via parasympathetic activity. This effect is blocked by introduction of atropine, a parasympatholytic agent[39].

1.4 Functional outcomes

1.4.1 Pain management

Pain is defined by the International Association for the Study of Pain as an "unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage". It is a vital function of the nervous system to provide a warning signal and trigger a response from the individual experiencing the pain. This signal is carried by nerve fibers from the location of the injury, through the spinal cord and to the brain where it is processed and interpreted. The perception of pain depends on many factors including one's individual pain matrix and as a result, is always a subjective experience.

The human body has a system to decrease the pain sensation after the warning information has been processed[40–43]. In this system, endogenous opioids play a preponderant role both by reducing ascending transmission of the nociceptive message and by descending inhibition from the brain to the spinal cord (**Figure 1**). At the peripheral level, endogenous opioids reduce the transmission of nociceptive impulses[44]. Descending modulations of pain arise from multiple areas including the somatosensory cortex, the amygdala, and the hypothalamus, and are projected into the periaqueductal grey (PAG). The PAG then projects onto the parabrachial nucleus, locus coeruleus and medulla, and then onto the spinal or medullary dorsal horns. When involved in this descending modulation, endogenous opioids act by reducing interneural signal transmission of the nociceptive message[29] and by inhibiting the release of GABA, thus resulting in abundant release of dopamine. Dopamine is a main actor in the feelings of pleasure, reward and euphoria and as such modulates the perception of pain, especially its affective and motivational aspects.

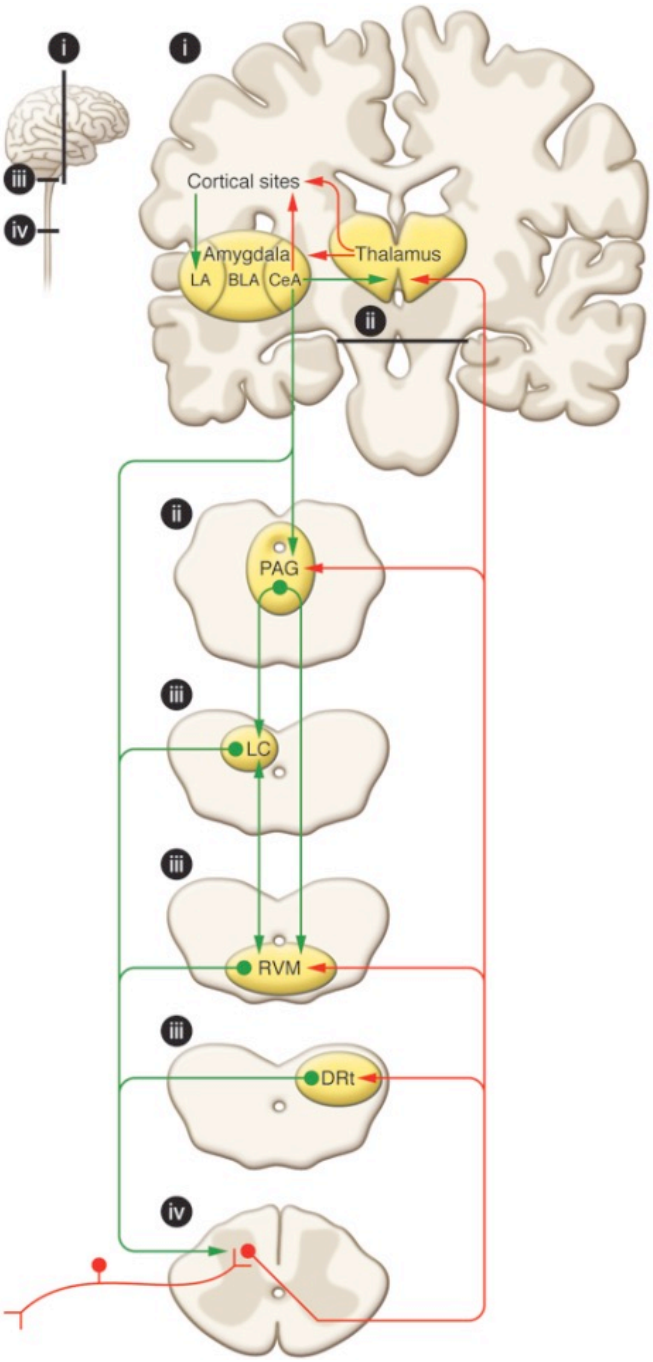

Figure 1. Schematic representation of pain modularity circuitry from Ossipov et al. (2010)[41].
Ascending (red) and descending (green) tracts are shown schematically. Areas labeled "i–iv" in the small diagram correspond with labeled details of the larger diagram. BLA = basolateral amygdala; CeA = central nucleus of the amygdala; DRt = dorsal reticular nucleus; LA = lateral amygdala; LC = locus coeruleus; RVM: rostral ventromedial medulla; PAG = periaqueductal gray region.

1.4.2 Stress and mood regulation

During the normal reaction to stress, the secretion of corticotropin-releasing hormone (CRH) stimulates POMC to release β-endorphin, which helps coping with pain and its emotional response[45]. However, prolonged stress leads to a gradual decrease of the peptide and β-endorphin levels over time.

Decreased levels of endorphins are found in populations suffering from anxiety and Post-traumatic-stress disorder (PTSD), especially combat-related PTSD in soldiers[46]. This pattern has been experimentally induced in rats: animals repeatedly exposed to the smell of a predator and thereafter showing a maladapted behavior had lower levels of β-endorphin compared to naïve rats[47].

Studies conducted in human and animals suggest a link between pathophysiology of major depressive disorder (MDD) and β-endorphin, with individuals suffering from MDD having lower levels of β-endorphins compared to healthy people[48]. Administration of opioid agonists in mice lead to antidepressant-like effects[49] and is successfully used for therapeutic benefits to relieve anxiety and depression in humans (for a review, see[50]).

Several mechanisms by which endorphins are involved in mood regulation have been identified. Endorphins regulate stress-coping strategies by interaction with the hypothalamic-pituary-adrenal (HPA) axis. In mice, mu-receptor agonists decrease freezing-like behaviors, while blocking of these receptors increase such passive behaviors[51].

Endorphins modulate hedonia and feelings of reward and satisfaction by interacting with the serotoninergic[47,52] and dopaminergic systems[53]. These aspects are found to be strongly affected in MDD patients. The interaction between β-endorphin and dopamine would be bi-directional, with neuronal effects of β-endorphin occurring both downstream and upstream to the dopaminergic synapse in the NAcc[18,19].

1.4.3 Sleep induction

Although "Morphine", the most famous opioid was named after the sleep god Morpheus, the mechanisms by which opioids induce sleep are sparsely investigated and described in the literature.

The first and perhaps most straightforward mechanism that could be considered to explain the sedative effects of endorphins is their anticholinergic properties. The rate of liberation of acetylcholine is significantly higher during wakefulness and REM sleep as compared to deep sleep[56,57], and this liberation is regulated by the endogenous opioid system[58]. This mechanism is part of the more global modulatory action of endorphins in the balance between sympathetic/parasympathetic activations. This whole modulating action (described in section 1.3.2.) *per se* promotes sleep induction.

The sleep-inducing effect of endorphins may also be due to their action on the ventrolateral preoptic nucleus (VLPO), a part of the brain that plays an important role in

sleep and wakefulness[59]. In animals, high doses of morphine seem to induce sleep through the opioidergic projection to the VLPO[60,61].

Pain, stress and (lack of) sleep are closely linked with interactions in all directions[62–66]. Dysfunction in one area negatively impacts the other two, just as improvement in any one has a beneficial effect on the function of the others.

1.4.4 Neuroplasticity

People that suffer from chronic stress[67,68], sleep deprivation[63]/chronic insomnia[64], and chronic pain (for example: chronic migraine[69]; chronic back pain[70], temporomandibular disorders[71]) have higher basal levels of glucocorticoids than non-sufferers.

Amongst the damage that continued activation of HPA axis on the body can inflict, prolonged exposure to glucocorticoids harms the brain. The impairing effect of glucocorticoids on neuroplasticity has been shown at different levels[72]. Amongst these are a decrease of long-term potentiation and its low-threshold form primed-burst potentiation[73], enhanced long-term depression[74], and atrophy of the apical dendrites on hippocampal cells[75]. Chronic stress and insomnia impair neurogenesis, by affecting cell proliferation, neuron differentiation and/or neuron survival[76]. Neuroimaging in humans also shows reductions in volume of some brain areas, particularly in the region of the hippocampus, in patients suffering from stress-related disorders such as PTSD[77], depression[78], and neurocitism[79] compared to normal control subjects. Chronic pain is associated with a reduction of brain grey matter volume or changes in cortical thickness[80,81] and functional reorganization of pain-related brain networks, including those related to the hippocampal formation[81–84].

As described above, endorphins have analgesic effects (1.4.1.), modify the sympathetic/parasympathetic balance in favor of a restful state (1.3.2), mediate the stress response (1.4.2) and promote sleep (1.4). As such, endorphins contribute to restore the natural conditions improving neuroplasticity. In addition, interactions between the serotonergic and endorphinic systems are well established[52], and serotonin leads to an increase in neuroplasticity[85,86]. Finally, endorphins have been the focus of research on neurogenesis in recent studies. Activities such that physical exercise or sexual activity were known both for leading to endorphin release and neurogenesis, therefore the release of endorphins during these experiences "may serve against elevated glucocorticoids and actually promote neuronal growth"[76]. *In vitro* studies have shown that endorphins and the activation of endorphins' target receptors increase proliferation of hippocampal progenitors[87], while blocking target receptors decreases the proliferation[88]. Koehl et al. (2008)[89] tested the effect of exercise on wild-type and β-endorphin-deficient mice. Their results show a strong and positive effect of exercise on cell proliferation and cell survival, leading to a net induction of adult neurogenesis in wild-type mice. On the other hand, the lack of β-endorphin completely blocked the running-induced increase in cell proliferation in β-endorphin-deficient runner mice compared to wild-type mice, which shows that β-endorphin released by exercise in wild-type mice is involved in their increased cell proliferation.

2 Millimeter wave therapies

2.1 Historical background

Millimeter Wave (MMW) therapy was developed in the 1970s, in the former Eastern-Bloc countries, at the intersection of biophysics, radio electronics and medicine. Teams of researchers conducted various experiments on the biological effects of MMW exposure and found painkilling results[90]. At the time, this necessitated the use of huge machines in dedicated rooms at a center people were obliged to visit to receive their treatment. In Eastern Europe, more than 3 million patients received MMW therapy for various conditions, in about 1000 centers[91].

However, the cost and bulk of such devices made them inconvenient for therapeutic use and precluded any ambulatory use. Their use was mostly empirical and no clear scientific explanation of the mechanism of action was identified. For these reasons, as well as the development of improved pharmaceutical solutions, MMW therapy stopped being used as a treatment of first intent, or even as an alternative to chemical medication.

After the collapse of the Eastern Bloc, several research teams kept studying MMW therapy for different applications, such as wound healing[92], diabetes[93], cancer[94] and the treatment of chronic pains[95]. Since then, the action of MMW on organic tissues as well as the physiological mechanisms by which they provoke analgesic effects have been better understood.

2.2 Functional principle

There are various sensory receptors situated in the superficial layers of the skin, the face, and the palms of the hands and feet being more densely innervated than others. Activation of these receptors sends signals from peripheral nerves via the spinal cord to the brain which processes the information. Endorphins are released centrally in response to sensitive peripheral stimulations, generally as a pain coping mechanism, even though pain

is not essential to trigger this response, as described in section 1.3.

Penetration depth of electromagnetic waves depends on their frequency such that their penetration depth decreases as their frequency increases (**Figure 2**). Millimeter waves lie within the frequency range of 30–300 GHz and do not penetrate skin beyond a fraction of a millimeter (0.3 – 0.5mm), i.e. the depth of cutaneous sensory receptors. During MMW therapy, skin is exposed to waves that carry enough energy to activate sensory receptors, but not enough to cause any injury. This painless nerve stimulation leads to an increase in the secretion of intracerebral endorphins, which have hypoalgesic effects.

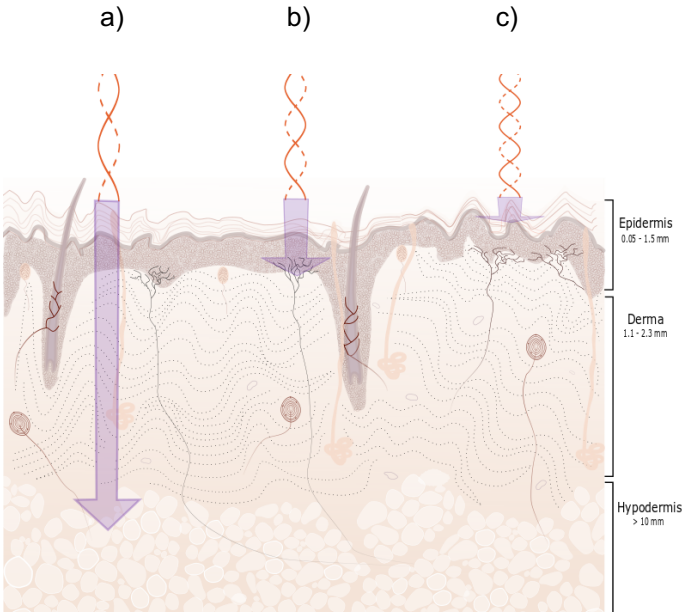

Figure 2. Skin exposed to waves frequency (a) lower than 30GHz, (b) 61.2GHz, (c) higher than 300GHz. Purple arrows represent energy absorption by the skin.

A series of experiments conducted by Radzievsky and colleagues from Temple University (Pennsylvania, USA), contributed to better understand the mechanism of MMW therapy. After demonstrating the suppression of pain sensation in humans exposed to MMWs[96] in a double-blind cross-over study, they showed that MMW-induced hypoalgesia is produced by the release of the endogenous opioids, by blocking this effect with naloxone, an opioid receptor antagonist[97]. They also demonstrated that the effect depends on the innervation density of the area exposed, the most innervated areas leading to the best results[98]. Further investigations confirmed the role of the peripheral nervous system when deafferentation of the area exposed to MMW totally abolished systemic hypoalgesia[99]. Lastly, they showed that hypoalgesic effects can't be replicated with laser-increased temperature alone[100], are power- and frequency-dependant, and that different types of pain do not respond in the same way to MMW therapy: a single exposure to MMW (15 min, frequency of 61.22 GHz and average incident power of 13.3 mW/cm^2) significantly reduced pain sensitivity in the models of acute and chronic non-neuropathic pain, but 10 exposures were necessary in a model of neuropathic pain in their study[101].

2.3 Scientific and clinical data

After the collapse of the Eastern Bloc, worldwide research teams continued to investigate MMW therapies in order to provide an understanding of the mechanisms involved in MMW-induced hypoalgesia in controlled experiments. Several articles have been published reviewing the "medical applications of MMWs"[102], their effects in "biology and medicine"[90], "in interaction with the human body"[103], "for pain therapy"[95]. These reviews, as well as other or later published articles, support the effectiveness of MMW therapies, in the absence of associated side effects, used either at *loco dolenti* or by dermal exposure remote from the pain's point of origin. Hereafter, we report results demonstrating the efficiency of MMW therapy in experimental and clinical pain, in both animals and humans, on different kinds of pain.

Experimental pain in animals:

Many animal studies have been conducted to investigate the mechanisms underlying MMW therapy (see the description of Radzievsky and colleagues' work in section 2.2) and determine the types of pain MMW therapy could Chuyan & Dzheldubayeva (2006)[104] showed analgesic effects of MMW (42.3 GHz, power rate density: 0.1 mW/cm^2, 30 minutes x 9 days) in different kinds of pain induced in rats, namely: **tonic somatic pain** with formalin injections, **visceral pain** with acetate injections (see also[105]), and **acute thermal pain** with the hot plate test. The authors concluded that "the analgesic effects are characterized by a certain universality" (p. 284).

Radzievsky, Gordiienko, Cowan, Alekseev, and Ziskin (2004)[100] investigated the effects MMW at a frequency of 61.22 GHz, an average power density of 13.3 mW/cm^2 applied on the nose during 15 minutes for one or 10 sessions, using the hot water tail-flick test as a model of **acute pain**, the cold water tail-flick test as a model of **chronic non-neuropathic pain**, and a chronic constriction injury in the sciatic nerve as a model of **chronic neuropathic pain**. They showed that a single session was sufficient to significantly reduce signs of chronic non-neuropathic pain and acute pain (see also[97]), even if less effectively in the latter. However, 10 sessions were required to reach a significant reduction of pain in the chronic neuropathic pain model.

Experimental pain in humans:
Radzievsky et al.[96] demonstrated a significant increase in withdrawal time in the cold pressure test (**acute pain**) in healthy human participants. In this study, after an exposure session of 30 min at 20mW/cm^2 on the lower third of the sternum, 60% of the exposed subjects showed an increase from 120% to 315% in the pain tolerance threshold.

Partyla et al. (2017)[106] used the same test with 20 healthy participants exposed to MMW at a frequency of 42.25 GHz and a power inferior to 17.2 mW/cm^2, applied on the sternum for 30 minutes. Participants' pain threshold increased significantly when participants were exposed to MMW, compared to baseline and exposure to white noise, but not when compared to sham exposure.

Clinical neuropathic pain:
Moazezi et al. (2008)[83] conducted a sham-controlled study on 51 patients with **Diabetic Sensorimotor Polyneuropathy**. Twenty-five patients received MMW sessions of 15 minutes at a frequency of 61.2GHz, and a power of 5.83 mW/cm^2, during 2 weeks, 6 times/week. They observed a significantly stronger decrease in the Toronto Clinical Neuropathy Score (TCNS) for MMW-exposed patients compared to sham-exposed patients.

Megdiatov et al. (1995)[107] investigated **trigeminal nerve neuralgia.** Patients were exposed to either MMW (27 patients) at a frequency of 42.2 GHz, at a power of 10mW/cm^2 for 15 minutes, applied to areas where branches of the affected trigeminal nerve approach skin, or to a sham device (25 patients), for 10 sessions in each condition. Nineteen of the 27 patients treated with MMW reported a decrease of the incidence and severity of pain attacks as opposed to 4/25 in the sham group.

Clinical joint pain:
Bakaliuk, et al. (1998)[108] tested patients with **osteoarthrosis**. On top of their conventional treatment, 114 patients were randomized either to MMW exposure (55–62 GHz and power density 10 mW/cm^2, applied to 4–5 acupuncture points around the affected joints, during 20 minutes, for a maximum of 10 sessions) or treatment only. Results showed reduced pain intensity, expressed as a joint pain index, diminished joint stiffness and lower level of C-reactive protein in the group treated with MMW compared to the control group. Benefits were felt as soon as the second or third treatment.

Usichenko, et al. (2003)[109]: Patients with **rheumatoid arthritis**: 12 patients were exposed to either group 1: MMW (frequency 54–64 GHz and power density 2.5 mW), group 2: sham, or group 3: MMW exposure as in group 1 and sham in random order, applied to the 4 acupuncture points situated near the affected joints, for a maximum of 40 minutes, for 5 to 9 sessions over 2 weeks. Patients from group 1 reported significant pain relief and reduced joint stiffness during and after the course of therapy. Patients from group 2 revealed no improvement during the study. Patients from group 3 reported changes regarding pain and joint stiffness only after real MW sessions.

Shliapak, et al. (1996)[110] tested children with **juvenile rheumatoid arthritis.** One hundred thirty-eight children were exposed to MMW with a frequency of 53.5 GHz, randomly assigned to either group 1: MMW applied to the affected joints for 30 min every day for 10 days, group 2: MMWs applied to acupuncture points bilaterally, irrespective of the location of the affected joints, 30 minutes by acupuncture point, for 6 sessions or group 3: MMW applied to 2 acupuncture points, one situated in the jugular notch and the second point chosen near the most affected (painful and swollen) joint. Intensity of joint pain decreased by 50% in all three groups, though these effects were more pronounced in group 3, duration of morning stiffness and circumference of the affected joints decreased as well, and the functional joint status improved in 80–90% of children.

Usichenko and Herget (2003)[111] conducted a pilot study with 12 patients with **diffuse connective tissue diseases** treated with MMWs applied on affected joints. Patients received between 5 and 10 sessions lasting 35 ±5 min with a frequency between 54 and 78GHz and a power of 9mW/cm^2. Pain intensity on a Visual Analogical Scale was significantly reduced for all patients after the 3rd exposure, and completely disappeared after the course of the treatment for 3 patients. Joint stiffness was also significantly reduced at the end of the treatment.

Post-operative pain:
Korpan and Saradeth (1995)[92] tested the effects of MMW therapy in **postoperative septic wounds** after abdominal surgery. Seventy-one patients received MMW at 37 GHz for 30 minutes/day for 7 days and 70 patients receive sham exposure. Patients from the MMW group showed 1.8 times more rapid wound clearance, 1.7 times earlier onset of wound granulation and 1.8 times faster onset of epithelization, and the average daily decrease of wound surface area in the treated patients was twice that of control subjects.

Pradahn, et al. (2014)[112] carried out a study with 120 patients who had to undergo a **cesarean section**. They showed that for 30 patients exposed to MMW (frequency: 38 GHz and power 40 mW/cm^2) for 3 consecutive treatment sessions of 30 minutes, over 3 days, the score of intensity of postoperative pain and the postoperative morbidity were significantly reduced, while postoperative mobility was increased, compared to the 90 patients of a control group.

Usichenko et al. (2008)[113] on the other hand, failed to find any significant beneficial effect of MMW therapy in patients with total **knee replacement surgery** (6 sessions of 30 minutes, frequency 50-75GHz and power density of 4,2mW/cm², applied on the knee wound) compared to patients exposed to sham. According to the authors, the lack of effect is likely to be due to the low power density used, and placement of the emitter on top of the bandage. Such a configuration would have prevented any sufficient penetration and the radiation absorption therefore would have taken place at the bandage level and not at the levels of the cutaneous nerve endings.

The medical literature is rich in studies showing the hypoalgesic effects of millimetre waves used under the same conditions as the Remedee One. These results, published as provocation studies, clinical trials or case reports, show good efficacy on several types of pain.

2.4 Remedee One: a technological breakthrough

Remedee Labs is developing technology resulting from two lines of progress: the identification of a biological mechanism of MMW action supported by scientific and clinical research, and a major step forward in the technology necessary to manufacture integrated hyper-frequency components.

Until the beginning of the 21st century, the size of emitters and power supplies precluded any extensive clinical development, especially if ambulatory use was desired. Recently, several applications using frequencies in the tens of GHz range have been developed and widely integrated in products and services. Communication technology has taken advantage of these increases in frequency, as higher bandwidth corresponds to higher data transfer rates. WiFi for instance, which has long been used at 2.4GHz and 5GHz, has recently adopted the 802.11ad standard using frequencies from 57GHz to 70GHz. Wireless backhaul and point-to-point communication systems have also made more and more use of the 60GHz band and benefit from the very high data rates it provides.

Radar has also benefitted from the increase in frequency, as shorter wavelengths allow for the detection of smaller objects and require smaller antennas. Long-range automotive radars now run at 77GHz and are used for cruise-control applications. New applications using miniaturized, personal radars, have been recently developed and integrated in consumer products, such as the Pixel 4 smartphone that uses the Google Soli radar technology as user gesture detection. Other personal radars use the high resolution offered by the small wavelengths to offer new functions such as contactless respiration rate monitoring or even contactless heartrate measurement for newborns.

These new applications come with the benefit of higher system integration and reduced device size, offered by the low power consumption of miniaturized integrated circuits. Microelectronics manufacturing technologies also drive down the costs of the components by several orders of magnitudes. Basic components such as amplifiers or oscillators in the tens of GHz range, that used to cost thousands of dollars are now available for just a few dollars, and are easier and cheaper to build into systems.

Such progress in technologies supporting frequencies and powers necessary for therapeutic use have enabled Remedee Labs to develop its patented Microelectronic Endorphin Trigger (MEET) module. This miniaturized module has been integrated into a wearable device – a wristband called "Remedee One" - making endorphin-stimulation therapy accessible for safe and efficient personal healthcare use.

3 Clinical trials

3.1 Remedee 0: Safety

3.1.1 Analysis of the literature

The safety of exposure to MMWs is well established and has been documented in many preclinical animal studies and clinical studies in human. For the electromagnetic spectrum ranging from 0 to 300 GHz, no study showed any cumulative or long-term effect[114].

Due to the superficial penetration of electromagnetic fields in the millimetric band, specific attention was paid to possible cutaneous and ophthalmological effects. It was of primary importance to determine what power density was perceptible, and that which would cause lesions. It was found in monkeys that energy levels as high as 5J/cm² were necessary to induce ocular lesions, while perception occurred for a few mJ/cm²[115–117]. Similarly, a factor of a 100 was identified between cutaneous perception/pain and tissular lesions[118]. *In vitro*, very high exposure levels (770 W/kg) are required to induce an inflammatory response (release of interleukin IL1β), which exceeds by several orders of magnitude those allowing perception *in vivo*[119]. Definitive evidence was drawn from human experiments testing the innocuity of the Active Denial System (ADS), a non-lethal weapon used for crowd dispersion in the USA. The specificity of ADS, which used MMW at significantly higher power levels than those used in the Remedee One, is to provoke pain sensations in order to make people flee, without any tissue damage[120].

3.1.2 Summary of the clinical trial

Remedee Labs' first clinical study "Remedee 0" was performed between October and December 2017 in collaboration with Eurofins/Optimed, a renowned French clinical research organization.

Remedee 0 is a phase I, randomized, placebo controlled, open, seven period, cross-over study designed to evaluate the tolerance and suppression of painful sensation caused by millimeter waves on healthy volunteers, in the exact same conditions of those emitted by the Remedee One wristband.

Ten volunteers (male and female aged from 18 to 65) were exposed seven times to MMW emissions (61.25 GHz frequency, 20 mW/cm^2 power density on a 5cm^2, on an area located on the palm side of the wrist). All participants were randomly exposed to MMWs for 30 minutes, 1h, 1h30, 2h, 3h, 4h, and also had 30 minutes of sham exposure. The cold pressure test was used as a measure of sensitivity to experimental pain and was performed 20 minutes after each exposure. No medication was allowed the week before and during the trial.

In this clinical trial, exposure durations up to 8 times longer than the typical treatment duration (30 minutes) were tested. Results showed the absence of any skin reaction, no significant increase of skin temperature or any other deleterious effects. After only 3 of 60 exposures were any adverse events reported (tingling sensation, slight itching or a sensation of warmth at the site of exposure).

Regarding hypoalgesic effects, results showed an overall increase of about 5-10 seconds in the latency before pain. Analysis of relative variations ([$Time_{exposure}$)-$Time_{sham}$]/$Time_{sham}$) showed increases present even for short duration exposures (50% for 30 minutes and 1h). The maximal mean increase (90%) was obtained for the 3-hour session but did not reach statistical significance. The small number of participants as well as the great inter-individual variability regarding pain perception may have precluded any observation of statistically significant results. Indeed, the perception threshold was spread from 11 to 76 seconds within the sham group, with a mean time of 28 seconds and a standard deviation 19 seconds.

Lastly, while the difference pre-post sham exposure led to a non-significant difference in heart rate measures, all exposure durations to MMW led to significant decreases. The 30-minute session led to an average decrease of 8.3 beats per minute and this decrease took more amplitude as the session durations increased up to the 3h-session, for which average heartbeat decrease was 11.5 bpm.

The results of this clinical trial demonstrate the safety of the Remedee solution and support the previous preclinical and clinical observations showing the analgesic effects of MMW therapy. Cardiovascular variations appear to be a very interesting indicator reflecting the central endorphin increase leading to a change in the sympathetic/parasympathetic balance.

3.2 Ongoing trials

Several medical studies conducted by Remedee Labs are ongoing to demonstrate the benefits of the solution in specific pathologies.

Post-surgical pain:
Heart surgeries are a source of pain which is usually treated with morphine. However, side effects of morphine include respiratory depression, post-operative sickness, delirium and cognitive dysfunction. Because most patients receiving this kind of surgery are elderly (mean age = 70), it is of critical importance to reduce morphine consumption while preserving an appropriate pain management.

This clinical trial (EPIKARD) assesses the efficiency of the Remedee One in decreasing morphine consumption in patients who underwent heart surgery (aortic valve replacement). In this trial conducted in collaboration with the Anesthesia services of CHU Grenoble, 35 patients will be exposed to MMW therapy using the Remedee One, receiving 2 sessions of 45 minutes pre-surgery and 4 to 5 sessions post-surgery (Remedee One group). Their consumption of self-administrated morphine at 24h and 48h post-surgery will be compared to the consumption of 60 patients receiving usual care (control group).

Results of this study are expected in the middle of the year 2020.

Rheumatic pain:
Prevalence of osteoarthritis in France is 17%. It is the second most common cause of invalidity and medical consultation after cardiovascular diseases. There is currently no cure for arthritis, only treatment for pain management which patients frequently report to be insufficiently effective.

This clinical trial (EPIKARTHROSE) enrolls 60 patients suffering from peripheral rheumatism (various forms of arthrosis, excluding vertebral arthrosis). This cross-over study takes place over 7 months, during which half of the patients follow their normal treatment for 3 months, and then receive MMW therapy using the Remedee One daily, 1 to 3 times a day, for 3 months. This order is counter-balanced for the other half of the patients, with a month of washout in between the two phases. At the end of each phase, patients will assess their level of pain on a Visual Analogical Scale and their functional capability. Because chronic condition like osteoarthritis affects patients' mood, sleep quality and quality of life, these criteria will also be assessed at the end of each phase.

Results of this long-term clinical trial are expected in 2021.

Pre-surgery rehabilitation:
Rhizarthrosis is a frequent condition in aging women and its prevalence should be growing further with global population ageing. In severe cases, surgery and post-surgery rehabilitation are recommended. Studies show that healthier states before joint replacement surgeries predict better post-surgical results, namely regarding pain, length of hospital stay, functional rehabilitation, psychological parameters. Though this pre-surgical rehabilitation is helpful in the long-term, it can be painful for patients when it is performed and therefore negatively perceived. The use of MMW therapy during pre-surgical physiotherapy rehabilitation would reduce the patients' pain, thus allowing them to apply their exercises more efficiently and give them more benefits. It would also increase the patients' perception of the rehabilitation and therefore their satisfaction.

This clinical trial (KINE-EPIK) assesses the efficacity of a combined pre-surgical physiotherapy and MMW therapy program in pain management following rhizarthrosis arthroplasty. Over 24 months, seventy-two patients will be included in the study: 36 patients in the pre-surgical rehabilitation program will receive 8 physiotherapy + MMW therapy sessions of 30 minutes each, over 4 weeks, and 36 patients will be part of a control group and will receive normal care, without any pre-surgical preparation. Patients will assess their level of pain on a Visual Analogical Scale after surgery and their functional capability between surgery and the 3 following months. Compliance to the program, as well as satisfaction of the patients will be also assessed.

Results of this long-term clinical trial are expected in 2022.

Migraine:
Migraine is a chronic condition that strongly impacts patients' quality of life. More than half the patients suffering from migraines have at least 2 crisis a month, for a third of patients, the crisis lasts at least 24h, and for half of patients, the intensity is such that it prevents them from carrying on any activity. The anticipatory anxiety of triggering a crisis also prevents patients from living a normal life and they often choose to limit normal activities such as social interactions.

The diagnosis of migraine can take a long time and pending diagnosis, patients tend to over use non-specific antalgics leading to the development of chronic headaches. The preventive pharmaceutical treatments currently available are tolerated by only half of patients and give positive results in only a third of patients.

Because migraine is a neuroplastic kind of pain, it is particularly resistant to pharmaceutic drugs and better results are obtained through neuromodulation. In this sense, the application of an easy-to-wear and easy-to-use MMW device such that the Remedee One is a promising option that can be used daily, as a prophylactic treatment against migraine.

In this clinical trial (MISTIC), patients with chronic migraine will use the Remedee One twice a day for 3 months. The number of days that the participant suffers from a migraine, and the intensity and duration of the migraine before and during treatment will be compared.

Results of this clinical trial are expected in 2021.

Fundamental investigations of the neural modulations following MMW stimulation using Sensory Evoked Potentials and Magnetoencephalography:
The analgesic effect of millimeter wave (MMW) therapy is due to the release of endogenous opioids - endorphins – in the brain. Due to their size, endorphins cannot cross the so-called "blood-brain barrier", a highly selective semi-permeable border between the brain and the blood vessels that irrigate it. Thus, a blood test to measure endorphin levels would not be representative of the intracerebral levels of endorphins following exposure to MMW therapy.

On the other hand, release of endorphins modulates the pain matrix by changing the neuronal activity and therefore a difference between activity before MMW stimulation and activity after MMW stimulation should be observable.

Magnetoencephalography (MEG) is a functional neuroimaging technique allowing the recording of the brain's magnetic field, and thereby of the cortical activation. In partnership with the CEA Clinatec (Grenoble, France) Remedee Labs will perform a study investigating the changes in cortical activity following the administration of painful stimuli before and after MMW stimulation using the Remedee One wristband.

Sensory Evoked Potentials (SEP) are neurophysiological markers allowing the exploration of the functioning of somatosensory pathways, from stimulated peripheral nerves to the primary somatosensory cortex, through the spinal cord and the brain stem. In addition to the MEG data, recordings of SEP before and after MMW stimulation with the Remedee One will allow us to establish a complete mapping of neural activity following MMW stimulation.

Results of these investigations are expected by the end of 2020.

Conclusion

Remedee Labs is developing technology allowing on-demand intracerebral release of endorphins via millimeter wave stimulation of the peripheral nervous system. The central secretion of opioids elicits hypoalgesic effects regardless of the biological nature or the anatomical origin of the pain.

Over the past three years, our multidisciplinary team, comprised of experts in electronic engineering, software development, machine learning, design, neurophysiology and medicine have developed the Remedee One, an easy-to-wear, watch-like device that stimulates one of the most innervated location of the body to maximize endorphin stimulation.

To ensure the proper and effective use of our device, the first step was to ensure its safety. A rigorous analysis of the literature, including fundamental studies conducted on animals and the assessment of the American Active Denial System on human volunteers, showed the absence of noxious effects of the exposure to MMWs. In addition, no scientific study or international norm (IEEE, ICNIRP) reports any long-term effect from electromagnetic millimeter wave exposures. Finally, the harmlessness of our device was confirmed in a clinical trial using the the Remedee 0 - a laptop controlled version of our MMW emitting device.

Remedee Labs is currently conducting several large-scale clinical trials using the Remedee One MMW emitting wristband, and more trials and scientific studies are in preparation. We aim to confirm and improve upon the hypoalgesic results presented in this document and publish our findings in peer-reviewed scientific journals. We believe that endorphin stimulation can have several other significant applications beyond pain management, including promoting well-being, alleviating sleeplessness, and managing chronic stress.

At the crossroads of neuroscience and advanced technology, Remedee Labs is developing an innovative solution for a safe home-based pain management. The Remedee One portable MMW emitter promises huge potential to help those suffering from chronic pain.

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