Remedee Labs

THE REMEDEE SOLUTION

SPRINGBOARD TO A HOLISTIC MANAGEMENT OF NOCIPLASTIC PAIN

White Paper | *Part 2*

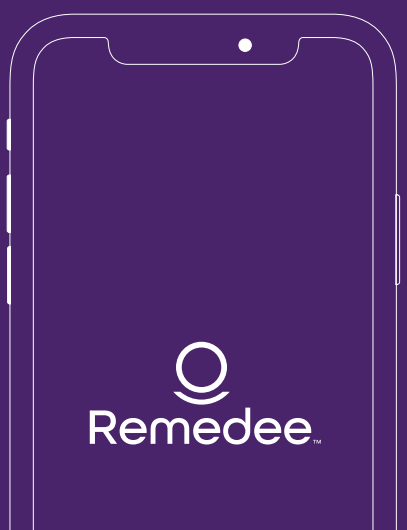

TABLE OF CONTENT

1. Chronic pain

1.1. Terminology

Pain is defined by the International Association for the study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". Pain is an alert signal seeking reaction from the sufferer to eliminate the cause of damage, and in that, is adaptative. When pain carries on for longer than the expected period of healing, then it is called "chronic pain" and considered dysfunctional.

Pain has long been considered as either *nociceptive*, i.e. arising from damage to non-neural tissues and being due to the activation of nociceptors, or *neuropathic*, i.e. caused by a lesion or disease of the somatosensory nervous system. In 2016, the IASP introduced the third terminology ***nociplastic pain*** to designate "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (Kosek et al., 2016, p. 1383).

The introduction of nociplastic pain came from the lack of an appropriate terminology for groups of patients showing chronic, rather widespread pain and/or hypersensitivity in apparently normal tissues, together with symptoms such that fatigue, sleep, memory and mood problems, and hypersensitivity to non-nociceptive sensory stimuli. Pain of those patients was then described as "pain of unknown origin" or "idiopathic". Advances made in neuroscience during the last decades brought enough evidence of modifications in cerebral activations, connectivity and structures in those groups of patients that justified to acknowledge their pain as a condition in itself (Kosek et al., 2016)

1.2. Nociplastic pain

1.2.1. Mechanisms

The expression "nociplastic" comes from the contraction of the words nociceptive and plasticity and intends to reflect changes in function of nociceptive pathways. Following an injury, "peripheral sensitization", a reduction in the threshold and/or an increase in magnitude of responsiveness at the peripheral ends of sensory nerve fibers, happens as a protective mechanism intending to preserve the area of injury and help recovery. This peripheral mechanism is accompanied by a collection of central mechanisms, both at the spinal and the supraspinal levels, designated as "central sensitization". Clinical observations such that hyperalgesia (i.e. increased pain from a stimulus that normally provokes pain) and allodynia (i.e. pain from a stimulus that does not normally provoke pain) are nowadays well explained by mechanisms such that expansion of sensory receptive fields (Billy & Walters, 1989), spinal cord reorganization(Wrigley et al., 2009), "wind-up" (Li et al., 1999; Mendell, 1966) and diminished descending modulation (Gebhart, 1986 ; Kwon et al., 2014; Ossipov et al., 2014). Moreover, image studies report changes in structure, with both decrease and increase of grey matter density in people suffering from chronic pain compared to controls (Apkarian, 2004; Smallwood et al., 2013), increased activity of brain regions involved in pain processing, together with an increased connectivity between those regions and that of emotion processing (Hsiao et al., 2017). Altogether, these mechanisms provide explanations to both the amplification and perpetuation of pain, as well as other central nervous system-deri ved symptoms like fatigue, sleep, memory and mood problems in people suffering from nociplastic pain.

1.2.2. Pain types overlap

The mechanisms described above and characteristic of nociplastic pain have been found in many chronic painful conditions both in isolation and in association with traditional - nociceptive or neuropathic - mechanisms. On one hand, there are pathologies that were previously described as "idiopathic" because no obvious traditional causes for people's symptoms could be found. Common among these are fibromyalgia and chronic widespread pain, complex regional pain syndrome, chronic low back pain, irritable bowel syndrome, chronic primary pelvic pain (for a review, see Fitzcharles et al., 2021). On the other hand, there are also conditions in which pain is said to be mixed because evidence for nociception or neuropathic lesions were found but couldn't explain patients' clinical pictures fully. Mechanisms of nociplastic pain, namely hypersensitization, has been shown in pathologies such that rheumatoid arthritis (Meeus et al., 2012) and osteoarthritis (Fingleton et al., 2015), endometriosis (Bajaj et al., 2003; Berkley et al., 2005), pain following cancer treatments (Nijs et al., 2016) and some forms of neuralgia (postherpetic neuralgia, (Schlereth et al., 2015).

1.2.3. Pain conditions overlap

In addition to the overlap between nociceptive and/or neuropathic and nociplastic pain, there is also a high degree of overlap and coprevalence between chronic pain conditions. To quote Maixner and colleagues "some groupings of patients share more clinical signs and symptoms across pain conditions than within a specific pain condition, consistent with the view that some overlap in etiological mechanisms underlies chronic overlapping pain conditions" (Maixner et al., 2016, p.98). Table 1 illustrates the overlap between common chronic pain conditions.

Table 1. Published estimates of overlap between index conditions and other chronic overlapping pain condition (from Maixner et al., 2015)

	Comorbidity (Percentage Overlap)				
Index Case Status	FM	IBS	TMD	CFS	VVD
FM		80[37]	75[82]	64[2]	NA
IBS	41[133]		16[57]	14[57]	NA
TMD	24[133]	64[2]		20[2]	NA
CFS	55[133]	58[37]	42[60]		NA
VVD	23[133]	25[75]	20[39]	8[75]	

Abbreviations: COPC, chronic overlapping pain condition; FM, fibromyalgia; IBS, irritable bowel syndrome; TMD, temporomandibular disorders; CFS, chronic fatigue syndrome; VVD, vulvodynia; NA, not applicable.

2. Chronic pain management

2.1. The biopsychosocial approach

The most current approach to consider the development of chronic nociplastic pain is the biopsychosocial model (Gatchel et al., 2014). eCohen et al. (2021) summarizes the rich literature describing the interaction of biological (genetics, sex, age, etc.), psychological (past experiences with pain, cognitive beliefs, catastrophism, anxiety, depression, coping skills, etc.) and social (financial barriers/health insurance, social support, etc.) factors in the development, perpetuation and worsening of pain. In return, nociplastic pain has biological (deconditioning, biomechanical problems, loss of grey matter, drug dependency, etc. psychological (anxiety and depression, cognitive impairment, learned helplessness, etc.) and social (withdrawal, dysfunctional relationships, isolation, increased suicide risk, etc.) impacts that contribute to maintain the condition (see Figure 1)

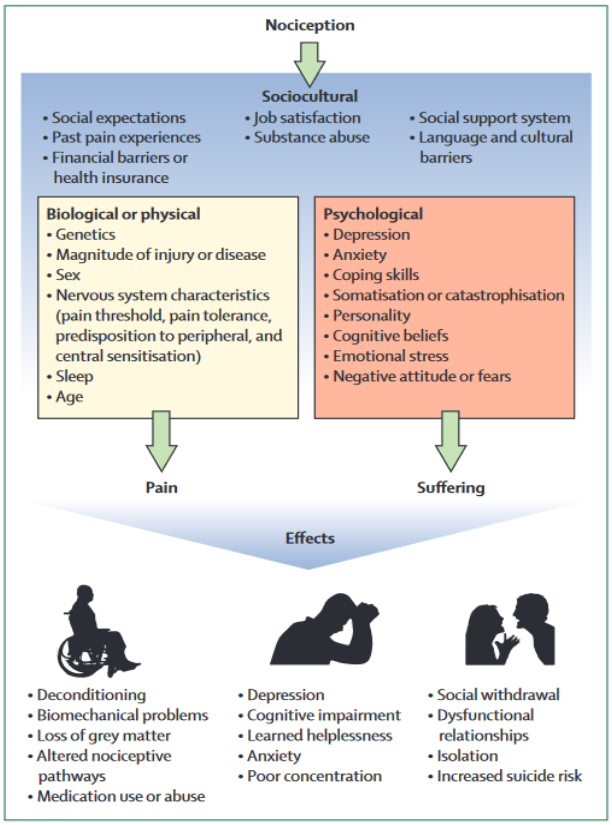

Figure 1. The biopsychosocial model of pain (illustration from Cohen et al., 2021)

An IASP-conducted task force (Guidelines for Desirable Characteristics for Pain Treatment Facilities, 1990) led to the definition of a required minimum of staff members and roles that should constitute an Interdisciplinary Chronic Pain management program (physician, nurse, psychologist, physical therapist, occupational therapist). Since, a review of interdisciplinary pain rehabilitation programs for chronic pain management has been published by Stanos (2012), describing in detail the interventions and the effects produced in 4 major programs established in the United-States. Nowadays, these programs developed throughout the world are recognized to provide the most efficacy, cost-effectiveness, and lack of iatrogenic complications compared to any other approaches for the treatment of chronic pain (Schatman, 2012).

2.2. Improving patients' quality of life

The consideration of pain as the integration of a signal in a bio-psycho-social human being that requires systemic approach also led to center efforts towards an improvement in quality of life rather than solely pain reduction (Niv & Kreitler, 2001). The economical perspective is another reason supporting this approach. Indeed, expensive drugs and health care together with the impact on work productivity and absenteeism require that the impact of chronic pain and its treatments be assessed in a broader way than the intensity of an individual's perceived pain.

Several standardized questionnaires are typically used to monitor quality of life, some being condition a-specific (for example, the World Health Organization Quality of Life Assessment Instrument (the WHOQOL), the Short Form Health Survey (SF-36, (Ware & Sherbourne, 1992) and shorter version SF12), the EQ-5D (Hurst et al., 1997) and others being condition specific (for example the Fibromyalgia Impact Questionnaire (FIQ, Burckhardt et al., 1991), The Roland-Morris Disability Questionnaire for back pain (RDQ, Stratford & Riddle, 2016); the Western Ontario MacMaster Osteoarthritis Index (Bellamy et al., 1988); the Migraine disability Assessment Scale (MIDAS, Stewart et al., 2000)). Those forms are useful both at the individual level to monitor the evolution of a patient's health, and at the group level to assess, analyze and compare treatment efficacy and health cost-effectiveness.

From the perspective of improving patient's quality of life, the recommendations regarding the management of nociplastic pain place non- pharmacological therapies at first line (American Society of Anesthesiologists Task Force on Chronic Pain Management, 2010; (Fitzcharles et al., 2021). Indeed, the modest benefit, adverse effects and drug dependencies associated with those treatments justify to limit their usage (Dowell et al., 2016). Experts recommend long-term approach with periodic follow-up to monitor evolution and make adjustments when needed, providing education to patients about biopsychosocial model and good lifetime habits, namely engaging in physical activity, balanced nutrition and weight management, sleep hygiene, and stress reduction. Approaches like cognitive-behavioral therapies to promote self-management are also strongly encouraged.

2.3. Digital interdisciplinary approach

The interdisciplinary approach recommended for chronic pain is not to be confused with multidisciplinary approach (Gatchel et al., 2014). While both involve several types of health care providers, the former implies coordination between interventions organized in a comprehensive program, "all providing care under one roof at the same facility" (Gatchel et al., 2014, p. 120). However, access to pain clinics and programs is not widely available. Schatman (2012) reports wait periods ranging from 1.3 to 18 months to access interdisciplinary pain management services amongst 13 developed countries, with

number of citizens per clinic ranging from 255,555 to 7,666,666. While these numbers already reflect the overloading of such programs, they don't take into account uneven geographic distribution, for many patients, they may fall outside a catchment area, or be unable to travel the distance necessary to access a program.

As described in section 2.1, interdisciplinary approach provides the best results in terms of chronic pain management but how sustainable are the benefits when the patients go home? Stanos (2012) displays results from the Chronic Pain Rehabilitation Program of Cleveland Clinic Foundation (Ohio, Unites-States). In 2010, while patients showed a mean improvement of 56.3% of their pain disability scores from admission in the program to discharge, they also showed a deterioration of their scores of 21.1% at 6 months from discharge and 25.9% at 1 year from discharge.

A digital approach can cover the gap both in terms of program availability and practitioner follow-up for patients. Digital health & wellness is a growing field driven by constant technological development. A Cochrane review assessed digital interventions' effects as "largely positive" in improving chronic patients' knowledge, feeling of social support, and clinical outcomes, compared to patients who did not use this kind of approach (Murray et al., 2005). Specifically, technology-assisted interventions have been shown to be efficacious for improving self-management of chronic pain in adults (Williams, 2011). Despite the heterogeneity of pathologies studied in some meta-analyses (e.g. Rosser et al., 2009), authors highlight the overlap in behaviors targeted for change, namely maladaptive cognition, physical activity and dietary management.

3. The Remedee solution as a springboard to a holistic management of nociplastic pain

3.1. The Remedee band

Remedee Labs has developed unique technology using millimeter waves (MMW) to stimulate subcutaneous nerve receptors in the wrist, which signal the brain, which in turn releases endorphins. The mechanistic and biological effects of MMW are well known and Remedee Labs has already demonstrated their hypoalgesic and parasympathetic effects, as well as the innocuity of its emitter device (see Remedee Labs White paper Volume I).

As an electronic alternative to medication allowing users to control their own pain management with no risk of overdose, the Remedee wristband is an "at home" non-molecular therapy which can be used without restriction or inconvenience. Patients are thus completely autonomous and responsible for their own therapy in terms of time and frequency.

Adherence to long-term therapy is a well-known problematic in people with chronic disease. According to the World Health Organization, 50% of people with chronic disease take their treatment as prescribed (Sabaté & World Health Organization, 2003). Poor adherence has consequences both on patient's quality of life and health economics. "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments" (Haynes et al., 2008). In their concept exploration of compliance, Rafii et al. (Rafii et al., 2014, p.165) state that "compliance is an intentional and responsible process of care in dyad level, in which patients and healthcare professionals make efforts to achieve mutually derived health goals collaboratively." Patients need several kinds of support: education, technical training, behavioral change support, emotional support, social support. It is also highlighted that adherence to treatment is a dynamic process that needs follow-up meetings to proceed to adjustments (Sabaté & World Health Organization, 2003, p.34).

In this context, the integration of health and wellness coaching to support patients and potentiate the effects of the Remedee band seemed relevant.

3.2. The Remedee Wellness solution

In 2021, Remedee Labs put its first wellness offer targeting people with fibromyalgia on the market. Fibromyalgia is a nociplastic condition characterized by chronic widespread pain, sleep disturbances, fatigue, and cognitive dysfunction, that impacts 2-4% of the general population.

People who purchased the Remedee Solution were given access to a Remedee wristband, a coaching program, a smartphone application and on-demand technical support. The offer also allowed them to try the device for a period of 2 months with full reimbursement if they were not satisfied with the solution. Through 3 phone calls (2h30) and their smartphone application, users received coaching providing:

i. education on MMW therapy, endorphins and device use optimization;
ii. Technical training on device usage;
iii. Incentivization and rewards for compliance;
iv. Monitoring and feedback on device usability, compliance and health status (using the Fibromyalgia Impact Questionnaire (FIQ) to measure quality of life, Pittsburgh Sleep Quality Index to measure sleep quality, and the Patient Global Impression of Change questionnaire (PGIC)).

Coaches were trained to be knowledgeable about fibromyalgia and similar conditions and about the scientific principles underlying the device's action. Coaches could monitor users' wristband usage through a monitoring console and discuss compliance with the users. The general recommendation was to perform 3 sessions a day, including one at bedtime or within an hour before bedtime, every day. This program onboarding 303 users led to high persistence, with 81.8% (248/303) users choosing to keep the Remedee Solution after 2 months. Amongst them, there were 91% active users (i.e. users who kept using their device) after 100 days, 82% active users after 150 days and 83% active users after 200 days. Overall, adherence was high, users performed 2.8 sessions/day on average over the 3 first months.

After 3 months of usage, 85.6% perceived their health status as being improved, from minimally to very much improved. After 3 months, 72.3% users showed a relative improvement

superior to 14%, which is considered as clinically significant according to Bennett et al. (2009). On average, users improved their FIQ total scores at D90 by 27.9%, relative to their scores at D0. Amongst users, 79.7% improved their sleep quality between D0 and D90. On average, users improved their PSQI total scores at D90 by 28.4%, relative to their scores at D0.

The FIQ dropped by 19.3 points on average between D0 and D90. For comparison, drug therapies that have been FDA approved in the USA, like duloxetine (Arnold et al., 2005), pregabalin (Zhang et al., 2021), or Milnacipran (Mease et al., 2009) showed a decrease of FIQ scores of -16.8, -11.1 and -17.7 respectively. Following that program, the FDA has granted its Breakthrough Device designation to Remedee Labs for its endorphin stimulation device for the management of fibromyalgia.

For a complete real-world evidence report of that project, see Remedee Labs' fibromyalgia white paper.

3.3. The Remedee Well digital solution

The success of the Remedee Solution encouraged Remedee Labs to build a digital version of its program, in order to manage patients more efficiently and provide access to the solution to more patients.

Remedee wellness coaches use a console that allows them both to monitor groups of patients (program progression, wristband usage, etc.) and to interact individually with them (chat messages, sending questionnaires and reports, adapting posology and wristband configuration, etc.)

Patients use the Remedee App that includes multiple functions supporting behavioral change (education content, incentivization, monitoring, feedback, visualization of performance, etc), to follow their program and track their wristband usage. The app also includes a chat, allowing users to exchange private messages with their coach, and an access to a community platform in which they can exchange with other users sharing a chronic pain background.

The digital offer designed and opened for fibromyalgia patients from October 2021, has been adapted and opened to patients with all sorts of nociplastic pain since June 2022.

At time of writing, 70.1% of users who started the Remedee program stayed on it for at least 3 months. Amongst 503 users assessed 3 months after the beginning of their program, 80.5% rated an improvement in their health, ranging between "little" improved to "very much" improved. These results, a year after the beginning of the digital program are very encouraging and the continuous development of the Remedee Solution will only allow better results.

3.4. Towards an interdisciplinary digital approach

While the interdisciplinary approach makes perfect sense from the life-time health and scientific perspectives, the long term approach required may not immediately appeal to patients overwhelmed by their debilitating symptoms. Thus, the first months of the Remedee program prepare the ground to a holistic change by helping patients get relief from their symptoms and create a constructive relationship with their coach. This involves helping patients become familiar with their device, the digital environment, and their coach. This work, together with helping them commit to and comply with the recommendations of their program, will build and monitor the improvement of their health until they have improved their health and reduced their symptoms to a noticeable and satisfying and can move on to set new goals. **Remedee is currently working on an interdisciplinary digital program that will involve sleep and nutrition management, as well as adapted physical activity**. It will also give access to meditation training. As recommended by health authorities (see section 2), the program will be built and ran by specialists who belong to the same team.

4. Clinical Trials and opening to other pathologies

4.1. Fibromyalgia

Following the positive feedback from Remedee Wellness users, Remedee Labs initiated a clinical trial to demonstrate the effectiveness of its solution in improving the quality of life of people with fibromyalgia. In a multicentric, randomized, controlled trial (FIBREPIK- NCT05058092), patients were dispatched into two groups: The Immediate group had access to the Remedee solution just after randomization in addition to standard of care, while the Delayed group carried on with standard of care for 3 months before receiving the Remedee solution. The Remedee solution included a Remedee band, to be used 3 times a day, and four coaching sessions performed through phone calls over the first two months of wristband usage. The effectiveness of the solution was assessed by measuring the evolution of the quality of life after 3 months (using the FIQ), compared between the two groups after 3 months.

All 170 patients were included in 6 months, and follow-up is underway. Results are expected in May 2023.

4.2. 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 osteoarthritis, only treatment for pain management which patients frequently report to be inadequate.

This clinical trial (Epikarthrose-NCT04590079) enrolled 60 patients suffering from peripheral rheumatism (various forms of arthrosis, excluding vertebral arthrosis). The cross-over study took place over 7 months, during which half of the patients followed their normal treatment for 3 months, and then received MMW therapy using the Remedee band daily, 1 to 3 times a day, for 3 months. This order was 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 assessed their level of pain on a Visual Analogical Scale and their functional capability. Because chronic conditions like osteoarthritis affects patients' mood,

sleep quality and quality of life, these criteria were also assessed at the end of each phase.

All patients were included within 13 months. Follow-up visits finished in August 2022, results are expected for December 2022.

4.3. 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 overuse non-specific antalgics leading to the development of chronic headaches. The preventative pharmaceutical treatments currently available are tolerated by only half of patients and give positive results in only a third of patients. Stress and lack of sleep are factors triggering migraine crisis and migraine often coexists with pathologies like fibromyalgia (Burch et al., 2019). The presence of nociplastic comorbidities may aggravate invalidity due to migraines. Therefore, therapies intending to diminish triggering factors, central sensitization and invalidating comorbidities, should reduce the global burden of the disease (deTommaso et al., 2016).

In a multicentric, randomized, placebo-controlled clinical trial (MISTIC-NCT04568252), patients with chronic migraine used the Remedee band or a sham device twice a day for 3 months. The number of days that the participants suffered from a migraine, and the intensity and duration of the migraine before and during treatment will be compared between groups.

Inclusions of the 140 patients from 6 centers were included up to July 2022. The end of study will be in February 2023 and final results are expected for June 2023.

For more information and updates about Remedee Labs' clinical trials, see https://remedeelabs.com/en/scientific-research/

Conclusion

During the last two years, Remedee Labs has extended its product from a millimetric emitting device towards a comprehensive program, supported by a digital platform and run by trained health coaches for the management of chronic pain. The current recommendations regarding nociplastic pain management leave no doubt that this holistic, digital approach is what's necessary to provide most patients with a long-term solution to improve their quality of life.

References

Apkarian, A. V. (2004). Chronic Back Pain Is Associated with Decreased Prefrontal and Thalamic Gray Matter Density. *Journal of Neuroscience*, *24*(46), 10410-10415. https://doi.org/10.1523/JNEUROSCI.2541-04.2004

Arnold, L. M., Rosen, A., Pritchett, Y. L., D'Souza, D. N., Goldstein, D. J., Iyengar, S., & Wernicke, J. F. (2005). A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain*, *119*(1-3), 5-15. https://doi.org/10.1016/j.pain.2005.06.031

Bajaj, P., Bajaj, P., Madsen, H., & Arendt-Nielsen, L. (2003). Endometriosis is associated with central sensitization : A psychophysical controlled study. *The Journal of Pain*, *4*(7), 372-380. https://doi.org/10.1016/S1526-5900(03)00720-X

Bellamy, N., Buchanan, W. W., Goldsmith, C. H., Campbell, J., & Stitt, L. W. (1988). Validation study of WOMAC : A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *Journal of Rheumatology*, *15*, 1833-1840.

Bennett, R. M., Bushmakin, A. G., Cappelleri, J. C., Zlateva, G., & Sadosky, A. B. (2009). Minimal Clinically Important Difference in the Fibromyalgia Impact Questionnaire. *The Journal of Rheumatology*, *36*(6), 1304-1311. https://doi.org/10.3899/jrheum.081090

Berkley, K. J., Rapkin, A. J., & Papka, R. E. (2005). The Pains of Endometriosis. *Science*, *308*(5728), 1587-1589. https://doi.org/10.1126/science.1111445

Billy, A. J., & Walters, E. T. (1989). Long-term expansion and sensitization of mechanosensory receptive fields in Aplysia support an activity-dependent model of whole-cell sensory plasticity. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *9*(4), 1254-1262.

Burckhardt, C. S., Clark, S. R., & Bennett, R. M. (1991). The fibromyalgia impact questionnaire : Development and validation. *The Journal of Rheumatology*, *18*(5), 728-733.

Cohen, S. P., Vase, L., & Hooten, W. M. (2021). Chronic pain : An update on burden, best practices, and new advances. *The Lancet*, *397*(10289), 2082-2097. https://doi.org/10.1016/S0140-6736(21)00393-7

Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. *JAMA*, *315*(15), 1624-1645. https://doi.org/10.1001/jama.2016.1464

Fingleton, C., Smart, K., Moloney, N., Fullen, B. M., & Doody, C. (2015). Pain sensitization in people with knee osteoarthritis : A systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *23*(7), 1043-1056. https://doi.org/10.1016/j.joca.2015.02.163

Fitzcharles, M.-A., Cohen, S. P., Clauw, D. J., Littlejohn, G., Usui, C., & Häuser, W. (2021). Nociplastic pain : Towards an understanding of prevalent pain conditions. *The Lancet*, *397*(10289), 2098-2110. https://doi.org/10.1016/S0140-6736(21)00392-5

Gatchel, R. J., McGeary, D. D., McGeary, C. A., & Lippe, B. (2014). Interdisciplinary chronic pain management : Past, present, and future. *American Psychologist*, *69*(2), 119-130. https://doi.org/10.1037/a0035514

Gebhart, G. F. (1986). Modulatory Effects of Descending Systems on Spinal Dorsal Horn Neurons. In T. L. Yaksh (Éd.), *Spinal Afferent Processing* (p. 391-416). Springer US. https://doi.org/10.1007/978-1-4684-4994-5_16

Haynes, R. B., Ackloo, E., Sahota, N., McDonald, H. P., & Yao, X. (2008). Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD000011.pub3

Hsiao, F.-J., Wang, S.-J., Lin, Y.-Y., Fuh, J.-L., Ko, Y.-C., Wang, P.-N., & Chen, W.-T. (2017). Altered insula–default mode network connectivity in fibromyalgia : A resting-state magnetoencephalographic study. *The Journal of Headache and Pain*, *18*(1), 89. https://doi.org/10.1186/s10194-017-0799-x

Hurst, N. P., Kind, P., Ruta, D., Hunter, M., & Stubbings, A. (1997). Measuring health-related quality of life in rheumatoid arthritis : Validity, responsiveness and reliability of EuroQol (EQ-5D). *Rheumatology*, *36*(5), 551-559. https://doi.org/10.1093/rheumatology/36.5.551

Kosek, E., Cohen, M., Baron, R., Gebhart, G. F., Mico, J.-A., Rice, A. S. C., Rief, W., & Sluka, A. K. (2016). Do we need a third mechanistic descriptor for chronic pain states? *Pain*, *157*(7), 1382-1386. https://doi.org/10.1097/j.pain.0000000000000507

Kwon, M., Altin, M., Duenas, H., & Alev, L. (2014). The Role of Descending Inhibitory Pathways on Chronic Pain Modulation and Clinical Implications. *Pain Practice*, *14*(7), 656-667. https://doi.org/10.1111/papr.12145

Li, J., Simone, D. A., & Larson, A. A. (1999). Windup leads to characteristics of central sensitization. *Pain*, *79*(1), 75-82. https://doi.org/10.1016/S0304-3959(98)00154-7

Maixner, W., Fillingim, R. B., Williams, D. A., Smith, S. B., & Slade, G. D. (2016). Overlapping Chronic Pain Conditions : Implications for Diagnosis and Classification. *The Journal of Pain*, *17*(9), T93-T107. https://doi.org/10.1016/j.jpain.2016.06.002

Mease, P. J., Clauw, D. J., Gendreau, R. M., Rao, S. G., Kranzler, J., Chen, W., & Palmer, R. H. (2009). The Efficacy and Safety of Milnacipran for Treatment of Fibromyalgia. A Randomized, Double-blind, Placebo-controlled Trial. *The Journal of Rheumatology*, *36*(2), 398-409. https://doi.org/10.3899/jrheum.080734

Meeus, M., Vervisch, S., De Clerck, L. S., Moorkens, G., Hans, G., & Nijs, J. (2012). Central Sensitization in Patients with Rheumatoid Arthritis : A Systematic Literature Review. *Seminars in Arthritis and Rheumatism*, *41*(4), 556-567. https://doi.org/10.1016/j.semarthrit.2011.08.001

Mendell, L. M. (1966). Physiological properties of unmyelinated fiber projection to the spinal cord. *Experimental Neurology*, *16*(3), 316-332. https://doi.org/10.1016/0014-4886(66)90068-9

Murray, E., Burns, J., See, T. S., Lai, R., & Nazareth, I. (2005). Interactive Health Communication Applications for people with chronic disease. *The Cochrane Database of Systematic Reviews*, *4*, CD004274. https://doi.org/10.1002/14651858.CD004274.pub4

Nijs, J., Leysen, L., Adriaenssens, N., Aguilar Ferrándiz, M. E., Devoogdt, N., Tassenoy, A., Ickmans, K., Goubert, D., van Wilgen, C. P., Wijma, A. J., Kuppens, K., Hoelen, W., Hoelen, A., Moloney, N., & Meeus, M. (2016). Pain following cancer treatment : Guidelines for the clinical classification of predominant neuropathic, nociceptive and central sensitization pain. *Acta Oncologica*, *55*(6), 659-663. https://doi.org/10.3109/0284186X.2016.1167958

Niv, D., & Kreitler, S. (2001). *Pain and Quality of Life*. https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1533-2500.2001.01016.x

Ossipov, M. H., Morimura, K., & Porreca, F. (2014). Descending pain modulation and chronification of pain. *Current Opinion in Supportive & Palliative Care*, *8*(2), 143-151. https://doi.org/10.1097/SPC.0000000000000055

Rafii, F., Fatemi, N. S., Danielson, E., Johansson, C. M., & Modanloo, M. (2014). Compliance to treatment in patients with chronic illness : A concept exploration. *Iranian Journal of Nursing and Midwifery Research*, *19*(2), 9.

Rosser, B. A., Vowles, K. E., Keogh, E., Eccleston, C., & Mountain, G. A. (2009). Technologically-assisted behaviour change : A systematic review of studies of novel technologies for the management of chronic illness. *Journal of Telemedicine and Telecare*, *15*(7), 327-338. https://doi.org/10.1258/jtt.2009.090116

Sabaté, E., & World Health Organization (Éds.). (2003). *Adherence to long-term therapies : Evidence for action*. World Health Organization.

Schatman, M. (2012). Interdisciplinary chronic pain management : International perspective. *Pain Clin Updates*, *20*(7), 1-5.

Schlereth, T., Heiland, A., Breimhorst, M., Féchir, M., Kern, U., Magerl, W., & Birklein, F. (2015). Association between pain, central sensitization and anxiety in postherpetic neuralgia. *European Journal of Pain*, *19*(2), 193-201. https://doi.org/10.1002/ejp.537

Smallwood, R. F., Laird, A. R., Ramage, A. E., Parkinson, A. L., Lewis, J., Clauw, D. J., Williams, D. A., Schmidt-Wilcke, T., Farrell, M. J., Eickhoff, S. B., & Robin, D. A. (2013). Structural Brain Anomalies and Chronic Pain : A Quantitative Meta-Analysis of Gray Matter Volume. *The Journal of Pain*, *14*(7), 663-675. https://doi.org/10.1016/j.jpain.2013.03.001

Stanos, S. (2012). Focused Review of Interdisciplinary Pain Rehabilitation Programs for Chronic Pain Management. *Current Pain and Headache Reports*, *16*(2), 147-152. https://doi.org/10.1007/s11916-012-0252-4

Stewart, W., Lipton, R., Kolodner, K., Sawyer, J., Lee, C., & Liberman, J. (2000). Validity of the Migraine Disability Assessment (MIDAS) Score in comparison to a diary-based measure in a population sample of migraine sufferer. *Pain*, *88*, 41-52. https://doi.org/10.1016/S0304-3959(00)00305-5

Stratford, P. W., & Riddle, D. L. (2016). A Roland Morris Disability Questionnaire Target Value to Distinguish between Functional and Dysfunctional States in People with Low Back Pain. *Physiotherapy Canada*, *68*(1), 29-35. https://doi.org/10.3138/ptc.2014-85

The Development of the World Health Organization Quality of Life Assessment Instrument (the WHOQOL) | SpringerLink. (s. d.). Consulté 28 octobre 2022, à l'adresse https://link.springer.com/chapter/10.1007/978-3-642-79123-9_4

Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-Item Short-Form Health Survey (SF-36) : I. Conceptual Framework and Item Selection. *Medical Care*, *30*(6), 473-483.

Williams, D. A. (2011). Web-Based Behavioral Interventions for the Management of Chronic Pain. *Current Rheumatology Reports*, *13*(6), 543-549. https://doi.org/10.1007/s11926-011-0212-8

Wrigley, P. J., Press, S. R., Gustin, S. M., Macefield, V. G., Gandevia, S. C., Cousins, M. J., Middleton, J. W., Henderson, L. A., & Siddall, P. J. (2009). Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. *Pain*, *141*(1), 52-59. https://doi.org/10.1016/j.pain.2008.10.007

Zhang, X., Xu, H., Zhang, Z., Li, Y., Pauer, L., Liao, S., & Zhang, F. (2021). Efficacy and Safety of Pregabalin for Fibromyalgia in a Population of Chinese Subjects. *Journal of Pain Research*, *14*, 537-548. https://doi.org/10.2147/JPR.S281483

About Remedee Labs

Based on 10 years of pre-clinical and clinical research, Remedee Labs has designed and developed the first endorphin stimulator for personal use. Building on the experience of its clinical partners, the company now uses its unique technology to offer the first patient-centered digital service platform for chronic pain management, working alongside medical practitioners.

Remedee Labs technology, embedded in the first endorphin stimulator wristband, stimulates the nerve endings of the wrist during 30 minutes session. In response to this painless nerve stimulation, the brain releases intracerebral endorphins recognized as the body's highly effective natural pain killer – in a safe, fast and simple way.

But chronic pain requires comprehensive treatment that is tailored to individual needs and provided by a specialized team. Remedee Labs' solution is the only holistic approach that combines innovative technology, digital solution, human support and therapeutic education placing the patient at the center of the treatment for a sustainable improvement of his quality of life.

Remedee Labs initial focus is Fibromyalgia a debilitating chronic condition that affects many aspects of healthy living and quality of life. In may 2022 FDA has granted Breakthrough Device Designation for fibromyalgia patients based on initial real-world evidence results. The initial results showed a clinically significant improvement in their quality of life (FIQ) and an improvement in their sleep quality (PSQI).

Additionally, Remedee Labs is expanding its range of services to address other chronic pain conditions. Early data suggests strong efficacy in reducing pain across a variety of pathologies through digitally stimulated endorphin pathways.