



ARE NON-INVASIVE BRAIN STIMULATION TECHNIQUES EFFECTIVE IN THE TREATMENT OF CHRONIC PAIN? – A COCHRANE REVIEW SUMMARY WITH COMMENTARY

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The aim of this commentary is to discuss from rehabilitation perspective the Cochrane Review “Non-invasive brain stimulation techniques for chronic pain” (1) by Neil E O’Connell, Louise Marston, Sally Spencer, Lorraine H DeSouza, Benedict M Wand¹, under the direct supervision of the Cochrane Pain, Palliative and Supportive Care Group. This Cochrane Corner is produced in agreement with *Journal of Rehabilitation Medicine* by Cochrane Rehabilitation.

Key word: pain; rehabilitation; Cochrane Review Summary

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BACKGROUND

Chronic pain (CP), defined as pain of duration longer than 3 months, affects 19% of adults in Europe, more likely women, older people, and persons with socio-economic deprivation; its prevalence is expected to largely increase in the next decades (2, 3). CP of moderate to severe intensity is a serious health condition which is associated with limitations in activity and participation, lower quality of life (QoL) and all-cause mortality. To date, CP management, mostly delivered in primary care, is largely unsatisfactory, as CP most often persists despite receiving care, and as most CP patients report dissatisfaction with current treatment (4). Brain stimulation techniques for CP seek to modulate brain activity in the areas of the brain involved in nociceptive

processing (i.e. the thalamus), and to facilitate descending nociceptive inhibitory mechanisms. They may possibly induce prolonged alterations in cortical excitability by long-term synaptic changes. Both invasive and non-invasive electrical brain stimulation techniques have produced preliminary evidence of providing pain relief, and are used for treatment of CP, although not routinely. Non-invasive techniques are easier, safer, and thus more widespread: in repetitive transcranial magnetic stimulation (rTMS) the cerebral cortex is stimulated by a coil applied to the scalp: electric currents are induced in the neurons by rapid change of magnetic fields. Transcranial direct current stimulation (tDCS), transcranial random noise stimulation (tRNS) and cranial electrotherapy stimulation (CES) – via clip electrodes attached to the patient’s earlobes) involve the application of low-intensity electrical current to the cerebral cortex. Reduced impedance non-invasive cortical electrostimulation (RINCE) applies an electrical current via scalp electrodes by specific stimulation frequencies (5).

NON-INVASIVE BRAIN STIMULATION TECHNIQUES FOR CHRONIC PAIN

(Neil E O’Connell, Louise Marston, Sally Spencer, Lorraine H DeSouza, Benedict M Wand, 2018)

WHAT IS THE AIM OF THIS COCHRANE REVIEW?

The aim of this Cochrane Review was to evaluate the efficacy of non-invasive brain stimulation techniques in the treatment of chronic pain.

WHAT WAS STUDIED IN THE COCHRANE REVIEW?

The review included 94 randomized controlled studies (with total of 2,983 participants): 42 of rTMS, 11 of

¹This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2018, Issue 4, Art. No.: CD008208, DOI: 10.1002/14651858.CD008208.pub5 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

The views expressed in the summary with commentary are those of the Cochrane Corner author and do not represent the Cochrane Library or Wiley.

CES, 36 of tDCS, two of RINCE, two of tRNS and one evaluating both tDCS and rTMS. This review addressed patients over the age of 18 years with pain of 3 months' duration or more. All interventions studied (rTMS, CES, tDCS, tRNS and RINCE) were compared to sham. The outcomes of interest were pain intensity (visual analogue or numerical rating scales), disability, QoL and adverse events.

SEARCH METHODOLOGY AND UP-TO-DATENESS OF THE COCHRANE REVIEW

Previous updates searched all databases from their inception to July 2013 (3). For this update, the Review authors searched for randomized and quasi-randomized studies published from July 2013 to October 2017 in CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, LILACS and clinical trials register.

WHAT ARE THE MAIN RESULTS OF THE COCHRANE REVIEW?

The review shows that:

- High-frequency single dose rTMS of the motor cortex may lead to small, short-term pain and QoL improvements, but no effect is likely to be clinically relevant (low-quality evidence); no evidence of effects was found for other rTMS protocols (very low to low-quality evidence).
- tDCS may reduce pain (very low-quality evidence) and improve QoL (low-quality evidence) in the short term when compared with sham, but studies were very small.
- CES is not effective for CP (low-quality evidence).
- Both for rTMS and tDCS, the studies were of very low to low quality, presenting small sample size, blinding issues, and other methodological limitations.
- Few studies clearly reported side effects; transient headache, nausea and skin irritation were frequently reported, both with real and sham stimulation, but also two cases of seizure occurred following real rTMS.

HOW DID THE AUTHORS CONCLUDE?

Similarly to the 2010 and 2014 reviews (3), the authors concluded that possible benefits and harms of all types of non-invasive brain stimulation are still uncertain, and that more rigorously designed, larger studies are needed; also, longer courses of stimulation must be investigated.

WHAT ARE THE IMPLICATIONS OF THE COCHRANE EVIDENCE FOR PRACTICE IN REHABILITATION?

CP is a common reason for seeking rehabilitation, and also a common symptom in patients undergoing rehabilitation for other acute and chronic conditions (6). CP is often associated with one or more chronic diseases. Anxiety, depression, and catastrophizing beliefs about pain are also associated with CP and with a poor prognosis. The bio-psycho-social model describes CP as the result of a complex interaction of psychological, social and organic determinants, and recommends a multidimensional, interdisciplinary approach to CP rehabilitation. Exercise is thought to address both physical and psychosocial components of CP, but severely affected patients are generally more resistant to exercise therapy (7). Further, more severe pain and greater number of pain sites increase the risk of developing severe CP at any site, highlighting the importance of direct pain management, both to relieve symptoms and to interrupt this vicious circle. Pain medication is often used in the integrated approach to the rehabilitation of those suffering from CP, but CP is often refractory to medical management, and guidelines regarding pharmacotherapy recommend caution, particularly when treating older adults. Therefore, it is possible that CP patients may be candidates for non-invasive brain stimulation, that could also produce fewer systemic effects (5). The generally low quality of trials does not allow strong recommendations for any of these techniques, and, to date, their clinical application should be restricted to a clinical research setting (1), but their further investigation, by larger, robust randomized controlled trials, is needed to establish the possible benefits of any of these relatively novel interventions to CP relief and rehabilitation.

For more information, see also a link to the Cochrane podcast: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008208.pub5/related-content/podcast/54792/>.

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