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Repetitive transcranial magnetic stimulation in the management of chronic neuropathic pain

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Repetitive transcranial magnetic stimulation in management of chronic neuropathic pain. [Repetitiv transkraniell magnetisk stimulering för behandling av kronisk neuropatisk smärta]

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1. Abstract

Background

Neuropathic pain (NP) is defined as pain caused by a lesion or a disease that affects the somatosensory system. Clinical conditions with chronic NP often result in severe restrictions of activities of daily living and a reduced health related quality of life (HRQoL), with a concomitant risk for permanent disability. The available therapies, medical as well as physical, often fail to relieve the pain and other symptoms. Invasive neuromodulation techniques can be considered when these therapies fail due to insufficient effect or intolerable side effects. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive procedure for stimulation of the cerebral cortex. It offers an option for better treatment of patients with neuropathic pain that is mainly of central origin. The response to rTMS has also been used to select patients who may be suitable for epidural motor cortex stimulation (MCS).

Objective

To evaluate whether rTMS can relieve pain better than placebo (sham treatment) in patients with chronic neuropathic pain, and whether the response to rTMS can predict the effect of MCS in these patients.

Methods

A systematic literature search was conducted in PubMed, Embase, the Cochrane Library, PsycInfo, and a number of HTA-databases. Two authors independently screened titles, abstracts and full-text articles for inclusion and extracted data. The certainty of evidence was graded according to the GRADE system.

Main results

Twenty-one randomised controlled studies were included in the assessment of pain reduction by rTMS. All of them evaluated the effect on pain with the use of visual analogue scales (VAS) (0 = no pain, 10 = worst possible pain), but no study reported on the effects on HRQoL. Three cross-sectional studies were included for analysis of the predictive value of rTMS for the response to MCS.

Effects of single session rTMS on pain

In twelve trials the weighted mean VAS score at baseline was 6.8 for active rTMS and 6.6 for sham rTMS, and the mean difference following treatment was -1.2 and -0.1, respectively. In eight of the 12 trials the reduction was statistically significant.

Conclusion: It is uncertain whether one single session of rTMS results in little or no reduction of pain in patients with chronic NP. Very low certainty of evidence (GRADE ⊕◯◯◯)

Effects of multiple session rTMS on pain

In nine trials the weighted mean VAS score at baseline was 6.4 for active rTMS and 6.2 for sham rTMS, and the mean difference following treatment was -2.1 and -0.8, respectively. In six of the nine trials the reduction was statistically significant.

Conclusion: Multiple sessions of rTMS may result in little or no difference in pain reduction in patients with chronic NP. Low certainty of evidence (GRADE ⊕⊕◯◯)

Accuracy of rTMS to predict the response to epidural MCS

Three studies reported data that could be used to calculate sensitivity and specificity. The specificity of rTMS to predict a good clinical response was 75 % and 71 %, respectively, in the two studies that defined a good response as a reduction in the pain score of more than 30 %. It was 100 % in the study that defined a good response as a pain reduction of more than 50 %. The corresponding sensitivity was 60 %, 74 % and 89 %. The positive predictive value was 90 %, 79 % and 100 %.

Conclusion: The response to rTMS may be a useful predictor of the response to MCS in patients with chronic NP. Low certainty of evidence (GRADE ⊕⊕◯◯).

Concluding remarks

The present HTA analysis shows that multiple sessions of rTMS may result in a reduction of NP compared with sham stimulation. There is still a lack of knowledge about the effects of rTMS and MCS on HRQoL A single test session with rTMS seems to be a fairly good predictor of the response to epidural MCS. Repetitive transcranial magnetic stimulation should most likely primarily be used as a test method to adequately select patients suitable for epidural MCS.

2. Svensk sammanfattning – Swedish summary

Bakgrund

Neuropatisk smärta uppstår som konsekvens av en skada eller sjukdom som påverkar det somato-sensoriska systemet, det vill säga känselsystemet. Tillstånd med kronisk neuropatisk smärta leder ofta till allvarliga inskränkningar i det vardagliga livet och till en nedsatt hälsorelaterad livskvalité, med risk för permanent medicinsk invaliditet. Farmakologisk behandling och fysioterapi lyckas sällan åstadkomma tillräcklig smärtlindring. Invasiva neuromodulerande tekniker kan övervägas då tidigare behandlingsförsök misslyckats eller orsakat intolerabla bieffekter. Repetitiv transkraniell magnetisk stimulering (rTMS) är en icke-invasiv metod att stimulera cerebrala cortex. Metoden kan användas för behandling framför allt av patienter som har neuropatisk smärta orsakad av en lesion i det centrala nervsystemet. Behandlingssvaret på rTMS har även använts för att utvärdera patienter som kan vara lämpliga för epidural stimulering av motor cortex (MCS).

Syfte

Att utvärdera om rTMS ger bättre smärtlindring än placebo (sham behandling) hos patienter med kronisk neuropatisk smärta, och om behandlingssvaret på rTMS kan användas för att adekvat välja ut patienter lämpliga för MCS.

Metoder

Under december 2015 med en uppdatering i juni 2016 gjordes systematiska litteratursökningar i PubMed, Embase, the Cochrane Library, PsychInfo och flera HTA-databaser. Minst två författare granskade titlar, abstrakts och fulltextartiklar, värderade studiekvalitet och extraherade data oberoende av varandra. Det vetenskapliga underlagets styrka bedömdes enligt GRADE-systemet.

Resultat

Tjugoen randomiserade kontrollerade studier inkluderades i utvärderingen av rTMS effekter på smärta. Samtliga använde sig av visuella analoga skalor där 10 innebar värsta möjliga smärta och 0 ingen smärta alls. Ingen av studierna rapporterade några data avseende hälsorelaterad livskvalitet. Tre tvärsnittsstudier inkluderades för analys av hur väl rTMS kan prediktera svaret på MCS.

Effekter på smärta av en enstaka behandling med rTMS

Tolv studier inkluderades i analysen. Det viktade medelvärdet av VAS-poängen före behandling var 6,8 för aktiv rTMS behandling och 6,6 för sham behandling. Efter behandling reducerades den med i genomsnitt -1,2 respektive -0,1. I åtta av studierna var reduktionen statistiskt signifikant.

Slutsats: Det är osäkert om en enstaka behandling med rTMS resulterar i smärtlindring hos patienter med kronisk neuropatisk smärta. Otillräckligt vetenskapligt underlag (GRADE ⊕◯◯◯)

Effekter på smärta av upprepad behandling med rTMS

Nio studier inkluderades i analysen. Det viktade medelvärdet av VAS-poängen före behandling var 6,4 för aktiv rTMS behandling och 6,2 för sham behandling. Efter behandling reducerades den med i genomsnitt -2,1 respektive -0,8. I sex av studierna var reduktionen statistiskt signifikant.

Slutsats: Upprepad behandling med rTMS kan resultera i viss eller ingen smärtlindring hos patienter med kronisk neuropatisk smärta. Lågt vetenskapligt underlag (GRADE ⊕⊕◯◯)

Prediktiv förmåga av rTMS avseende behandlingssvar på epidural MCS

Tre studier har rapporterat data som kunde användas för beräkning av sensitivitet och specificitet. Specificiteten av rTMS att förutsäga ett bra kliniskt svar var 75 % respektive 71 % i de två studier där ett bra svar definierades som en reduktion av VAS poäng med minst 30 %. Specificiteten var 100 % i studien som definierade ett bra behandlingssvar som en reduktion på mer 50 %. Sensitiviteten i de tre studierna var 60 %, 74 % och 89 %. Det positiva prediktiva värdet var 90 %, 79 % and 100 %.

Slutsats: Behandlingssvaret på rTMS kan vara en bra prediktor av svaret på epidural MCS. Lågt vetenskapligt underlag (GRADE ⊕⊕◯◯)

Sammanfattande bedömning

Upprepad behandling med rTMS kan ge viss smärtlindring hos patienter med kronisk neuropatisk smärta. Det saknas kunskap om dess effekter på hälsorelaterad livskvalitet. Behandlingssvaret på en enstaka rTMS kan användas för att identifiera patienter som kan vara lämpliga för epidural MCS. Repetitiv transkraniell magnetisk stimulering bör tillsvidare primärt användas som metod att adekvat välja ut patienter som är lämpliga för epidural MCS.

The above summaries were written by representatives from the HTA-centrum. The HTA-report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers, and is ended with a concluding summary.

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3. Summary of Findings

Repetitive transcranial magnetic stimulation in patients with chronic neuropathic pain.
Active versus sham treatment

Outcome variable	Study design Number of studies	Absolute effect VAS (0-10) [1]		Relative effect VAS [2]	Certainty of evidence GRADE*
Pain Visual Analogue Scale	RCT				
Single session rTMS	12	Active Baseline: (weighted mean): 6.8 Mean change (Post-Pre): - 1.2	Sham Baseline: (weighted mean): 6.6 Mean change (Post-Pre): -0.1	- 15 % versus - 1 %	⊕◯◯◯ Very low[3]
Multiple sessions rTMS	9	Active Baseline: (weighted mean): 6.4 Mean change (Post-Pre): - 2.1	Sham Baseline: (weighted mean): 6.2 Mean change (Post-Pre): -0.8	- 28 % versus - 10 %	⊕⊕◯◯ Low[4]
Health related quality of life	RCT 0				
Medication use	RCT 0				

Footnotes:

1. Calculated average of the reported mean VAS values reported in seven single session and eight multiple session trials.
2. Calculated average of the relative reduction in VAS score reported in 11 of the 12 single session and nine multiple session trials. In eight of the 12 trials of single session of rTMS the difference in pain reduction between active and sham was statistically significant. In six of the nine trials of multiple sessions the difference in pain reduction between active and sham was statistically significant.
3. Serious inconsistency due to the variability in the effect size, serious study limitations, and some uncertainty with regard to directness and precision.
4. Some inconsistency due to the variability in the effect size, and some uncertainty with regard to precision.

Repetitive transcranial magnetic stimulation in patients with chronic neuropathic pain.
Prediction of response to MCS

Outcome variable	Study design Number of studies	Sensitivity	Specificity	Positive predictive value		Negative predictive value	Certainty of evidence GRADE*
rTMS response and MCS response	Case series						
	2(3)[5]	60 - 74 %	71- 75 %	79 – 90 %		33 – 65 %	⊕⊕◯◯ Low[6]

Footnotes:

5. Two studies defined a good response as at least a 30 % pain reduction, and the third study as more than 50 % pain reduction. The data in the SoF table are from the studies with the cut-off of 30 %.
6. Some uncertainty with regard to directness, some study limitations, some uncertainty with regard to precision.

4. Abbreviations/Acronyms

ADL	Activities of daily living
CNS	Central nervous system
DBS	Deep brain stimulation
EAN	European Academy of Neurology
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
MCS	Motor cortex stimulation
M1	Primary motor cortex
NP	Neuropathic pain
HRQoL	Health related quality of life
RCT	Randomised controlled trial
PNS	Peripheral nervous system
rTMS	Repetitive transcranial magnetic stimulation
SCS	Spinal cord stimulation
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analogue scale
VGR	Region Västra Götaland

*Certainty of evidence

High ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

5. Background

Chronic neuropathic pain

Neuropathic pain (NP) is defined as pain caused by a lesion or a disease that affects the somatosensory system (Jensen et al., 2011). It involves a variety of conditions and often becomes chronic in character (Baron, 2009). Most patients are managed in primary care, and only a minority are referred for specialist clinical assessment and diagnostic work-up. The available therapies often fail to relieve the pain when the symptoms become chronic. Clinical conditions with NP often result in severe restrictions of activities of daily living (ADL) and a reduced health related quality of life (HRQoL), with a concomitant risk for permanent disability. Patients with chronic NP tend to retire early from work, and some individuals develop drug abuse.

Chronic NP poses a major treatment challenge. It can be treated pharmacologically, with physiotherapy, or with non-invasive or invasive methods. All invasive interventional neuromodulation techniques are most likely underused in treating NP resistant to conventional non-invasive therapies. This is probably due to their high costs, suboptimal awareness and knowledge among physicians about these techniques, but also due to the limited evidence of their effectiveness.

Prevalence and incidence

The prevalence and incidence of chronic NP in Region Västra Götaland (VGR) are not known. Based on international data best estimates of the prevalence of pain with neuropathic characteristics in a general population are between 7 % and 10 % with an annual incidence of around 1 % (Dieleman et al. 2008; van Hecke et al. 2014). In VGR this would correspond to a prevalence of about 116 000 patients, and an annual incidence of about 16 000 patients. However, these estimates are uncertain due to varying diagnostic criteria, and the wide heterogeneity of the available epidemiological studies.

Present treatment of chronic neuropathic pain

First line therapy

There is no causal treatment available for chronic NP. Symptomatic first line therapies consist of various drug strategies that can be managed by different medical specialties such as primary care, orthopaedics, neurology, neurosurgery, and hand surgery. Drug treatment can be combined with acupuncture and non-invasive neuromodulation therapies, such as transcutaneous electric nerve stimulation (TENS). Only a small fraction of patients who suffer from chronic NP are referred to, and managed by, highly specialized multidisciplinary pain treatment teams.

Interventional neuromodulation

Invasive neuromodulation techniques can be considered when drug therapies fail due to insufficient effect or intolerable side effects. These therapies are mainly managed by neurosurgeons and anaesthesiologists. Modern implantable technology is used to deliver long-term electric stimulation to the nervous system. This is a change from earlier treatment strategies with ablative procedures towards reversible neuromodulation.

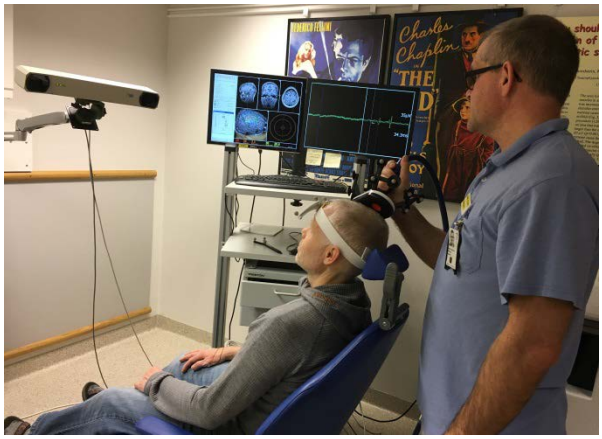
Patients with chronic NP generated by lesions in the peripheral nervous system (PNS), i.e. the nerve roots or peripheral nerves, can be treated with spinal cord stimulation (SCS) or subcutaneous peripheral nerve stimulation (Deer et al., 2014). Spinal cord stimulation is today the most commonly used interventional neuromodulation technique for chronic NP. More than 40,000 stimulators are implanted worldwide each year. Electrodes are implanted into the epidural space of the spinal column. The dorsal columns of the spinal cord are activated by the electric stimulation in order to block transmission of painful stimuli to the brain. This method is mainly used in the subset of patients who develop new or still have persistent pain after spinal surgery.

Patients with chronic NP due to lesions within the central nervous system (CNS), such as post-stroke pain, and pain after spinal cord injuries, will not benefit from SCS. The available non-pharmacological treatments for NP of CNS origin include electrical deep brain stimulation (DBS) and epidural motor cortex stimulation (MCS). Deep brain stimulation targets various nuclei of the thalamus, and epidural MCS primarily targets the primary motor cortex (M1) in the brain. Both are advanced, intracranial interventions that require neurosurgical expertise, and like SCS, involve implantation of electrodes and a nerve-stimulator.

Deep brain stimulation generally yields poor results in patients with chronic NP and is used only in the small subset of pain patients in whom other interventional methods have failed. Epidural MCS has been shown to be beneficial for selected patient groups with chronic NP. It has only sporadically been used mainly due to difficulties to select and target the proper parts of the cerebral cortex in order to achieve optimal pain relief.

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive procedure for stimulation of the cerebral cortex. It induces immediate and lasting changes in cortical excitability, and activates cortical structures via electrical currents induced by a transcranial magnetic field. The technology has been used in treatment of psychiatric disorders and chronic NP refractory to conventional pharmacological and physical therapy. The procedure is usually performed in an out-patient setting, and does not need a fully equipped operating room. Patients are normally awake during the procedure and no equipment for anaesthesia is needed.



The effects of rTMS upon various types of pain, including NP, have been evaluated in several studies. In most of them, M1 has been the target of stimulation, but other areas such as the dorsolateral prefrontal cortex have also been targeted. The frequency of stimulation, varying between 5 to 20 Hz, and the orientation of the stimulating coil are considered as the most crucial variables to achieve a good response. The procedure has been reported to be safe and the most commonly reported side effect has been a transient headache. The contraindications to rTMS include epilepsy, presence of a brain tumour, and the use of a cardiac pace-maker.

The therapeutic use of rTMS in patients with chronic NP, who are refractory to pharmacological treatment, is limited by the short duration of the induced effects. Studies with high frequency rTMS were initially based on a single stimulation session lasting for 10 - 20 min. This was reported to induce a delayed (by 2-4 days) analgesic effect that lasted for only 6 - 8 days. However, prolonged effects can be obtained by repeated rTMS sessions daily for several weeks.

The response to rTMS has been used to select patients who may be suitable for epidural MCS, which induces a larger and more longstanding pain relief than non-invasive techniques for stimulation of M1 (Lima and Fregni, 2008). At the Department of Neurosurgery, in collaboration with the Department of Clinical Neurophysiology, Sahlgrenska University Hospital, the rTMS technique has been applied in a few patients with post-stroke chronic NP. After a first clinical assessment, including a magnetic resonance imaging scan for detailed imaging of the brain, the patients were treated with rTMS in an outpatient setting. If a patient responded positively with pain reduction following rTMS, the MCS procedure was usually carried out within 3 to 8 months.

Neuromodulation strategies to treat chronic NP with rTMS are increasingly used internationally. Therefore, it is important to evaluate whether rTMS can form a basis for the decision to proceed with MCS, and to consider if rTMS should be implemented within the treatment algorithm for chronic NP in VGR.

Clinically relevant pain reduction

It is generally agreed that a clinically relevant reduction of pain in patients with various causes of chronic pain syndromes should be a reduction of no less than 30 % compared to the status before the initiation of a pain relieving therapy (Farrar et al., 2001; Ostelo et al., 2008).

The normal pathway through the health care system and current wait time for medical assessment and treatment

Patients who may be eligible for interventional pain treatment are generally referred to the Department of Neurosurgery, Sahlgrenska University Hospital, Göteborg, from primary care units, rehabilitation clinics, pain clinics, orthopaedic surgeons, and neurologists. The present wait time for assessment is normally less than three months. The time from assessment and diagnostic work-up to treatment has varied between 6 and 18 months during the last years. The long waiting time for treatment is mainly due to the heavy burden on the operating neurosurgical unit at the hospital.

Patients treated with DBS and MCS are exclusively managed at the Department of Neurosurgery, Sahlgrenska University Hospital, Göteborg. At the time of implantation of electrodes these patients are generally hospitalized for three to five days in the neurosurgical ward where also the initial programming of the stimulating devices is performed.

Number of patients per year who undergo invasive neuromodulation

Approximately 70 new patients with NP are treated annually with implantation of SCS devices in VGR. Forty patients are managed by the Department of Neurosurgery and the rest by the other two implanting units (see above).

Deep brain stimulation and MCS are both used infrequently for treatment of NP in VGR. The annual numbers of new patients are in the range of only one to three for each of these therapies. The use of MCS will most likely increase if the test procedures to adequately select suitable patients are improved. Repetitive TMS has the potential to be such a non-invasive screening tool.

Presently, rTMS can be expected to screen 10 - 20 patients annually at Sahlgrenska University Hospital for suitability for MCS. It is likely that referrals involving this patient category will increase.

Present recommendations from medical societies or health authorities

There are no regional or national guidelines for interventional treatment of patients with NP. Spinal cord stimulation is a well-established method and was assessed to have moderately strong scientific evidence for certain types of NP in the HTA-report 'Methods for treating chronic pain' by the Swedish Council on Health Technology Assessment in Health Care (SBU; 2006, report 177/1+2). In that report DBS and MCS for pain treatment were both assessed to have limited scientific evidence.

The European Academy of Neurology (EAN) recently updated the guidelines of the European Federation of Neurological Societies on central neurostimulation therapy in chronic pain (Cruccu et al., 2016). Based on The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) classification (Atkins et al., 2004; GRADE Working group) it was concluded in these guidelines that there is a weak recommendation for MCS and for rTMS of M1 in treatment of chronic NP.

6. Objective

Questions at issue:

Does rTMS relieve pain better than placebo (sham treatment) in patients with chronic NP, and can the response to rTMS predict the effect of MCS in these patients?

PICO 1 P= Patients, I= Intervention, C= Comparison, O=Outcome

P = Patients with therapy-resistant NP originating from lesions in the central or peripheral nervous systems
I = Active rTMS targeting the primary motor cortex
C = Sham/placebo treatment
O = Critical for decision making
Pain relief assessed by validated scales
Important for decision making
HRQoL according to validated scales
Medication use

Complications and adverse effects

PICO 2 P= Patients, I= Index test, C= Comparison/Reference test, O=Outcome

P = Patients with therapy-resistant NP originating from lesions in the central or peripheral nervous systems
I = Response to rTMS (clinically relevant pain reduction: yes/no)
C = Response to epidural MCS (clinically relevant pain reduction: yes/no)
O = Critical for decision making
Sensitivity and specificity*
Important for decision making
Positive and negative prediction value of rTMS for MCS in pain treatment*

*Based on a clinically relevant pain reduction defined as a reduction of more than 30 %. The severity of pain was estimated by validated scales.

7. Methods

Systematic literature search (Appendix 1)

During December 2015, with an update in June 2016, two authors (TS, AL) performed systematic searches in PubMed, Embase, the Cochrane Library and PsycInfo. The web-sites of SBU, Kunnskapssenteret and Sundhedsstyrelsen were also searched. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. The same two authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the participants of the project group. All authors read the articles independently of one another and it was finally decided in a consensus meeting which articles should be included in the report.

Critical appraisal and certainty of evidence

The included studies and their design and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are presented in Appendix 3. The studies included in the report were critically appraised using checklists that were modified from the ones used by Swedish Council on Health Technology Assessment (SBU). The results and the assessed quality of each article are summarised per outcome in Appendix 4. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 7). The certainty of evidence was defined according to the GRADE system (Atkins et al., 2004).

Ongoing research

A search in Clinicaltrials.gov 2016-09-29 using the search terms ***(transcranial OR cortical OR cortex OR "direct current") AND stimulation AND pain***.

8. Results

Systematic literature search (Appendix 1)

The literature search identified 1594 articles after removal of duplicates. After reading the abstracts 1476 articles were excluded. Another 68 articles were excluded by two authors after reading the articles in full text. The remaining 50 articles were sent to all participants of the project group, and 28 articles (21 randomised controlled trials, RCTs, three cross-sectional studies, and four case series) were finally included in the assessment (Appendix 2).
In addition, one systematic review was commented upon.

The effect of repetitive transcranial magnetic stimulation of the primary motor cortex (PICO 1)

In 2014 O'Connell et al. published an updated version of their first Cochrane review on "Non-invasive brain stimulation techniques for chronic pain" (O'Connell et al., 2014). Their literature search included RCTs published before August 2013, and was not restricted only to NP but included trials of all types of chronic pain. They concluded that single doses of high-frequency rTMS of the motor cortex may have small short-term effects on chronic pain, but the effects did not meet the predetermined threshold of minimal clinical significance. In a meta-analysis that only included effects of rTMS specifically in patients with chronic NP it was found that active rTMS reduced pain by 20 % (95% confidence interval for the relative risk reduction was -0.27 to -0.12) in comparison to sham treatment. With regard to trials of multiple sessions of rTMS they concluded that studies had not consistently demonstrated effectiveness, and therefore there was a need for larger, rigorously designed studies, particularly of longer courses of stimulation.

Critical outcomes for decision-making

Pain

The effect of rTMS on pain was studied in 21 RCTs. Twelve of them evaluated the effect of one single session of rTMS, and nine after multiple sessions (varying from two to 10 sessions).

- ***Single session rTMS (Appendix 4:2)***

All 12 RCTs had a cross-over design. A total of 301 patients were included. The majority of the patients suffered from post-stroke pain or pain from a spinal cord injury. There were some study limitations. The randomisation procedure was not clearly presented in some of the studies, and in some of them it was unclear whether the assessment of pain was blinded. There was also some uncertainty with regard to the directness since the selection of patients was not adequately described in most of the trials.

The weighted mean pain score, measured by the visual analogue scale (VAS), at baseline was 6.8 for active rTMS and 6.6 for sham rTMS, and the mean change following treatment was -1.2 and -0.1, respectively. In eight of the 12 trials the difference in pain reduction between active and sham rTMS was statistically significant. In four trials no significant difference was observed. A simple average calculation of the relative reduction in the pain VAS score, without taking into consideration the variability in the individual trials, yielded a reduction of 15 % for active rTMS and 1 % for sham rTMS.

Conclusion: It is uncertain whether one single session of rTMS results in little or no reduction of pain in patients with chronic NP. Very low certainty of evidence (GRADE ⊕◯◯◯).

- ***Multiple sessions rTMS (Appendix 4:3, Appendix 4:4)***

Three of the RCTs used a cross-over design and six used a parallel group design. A total of 328 patients were studied. The most common cause of the pain was a previous stroke or a spinal cord injury.
All trials reported that active rTMS resulted in a greater numerical reduction in the pain score than sham rTMS. However, there were some inconsistencies with various magnitudes in both the absolute and the relative reduction after treatment, as well as of the difference between active and sham stimulation in the nine trials.

The weighted mean VAS score at baseline was 6.4 for active rTMS and 6.2 for sham rTMS, and the mean difference following treatment was -2.1 and -0.8, respectively. In six of the nine trials the difference in pain reduction between active and sham rTMS was statistically significant. In six of nine trials the difference between active and sham rTMS was statistically significant. A simple average calculation of the relative reduction in the pain VAS score, without taking into consideration the variability in the individual trials, yielded in a reduction of 28 % for active rTMS and 10 % for sham rTMS.

Conclusion: Multiple sessions of rTMS may result in little or no difference in pain reduction in patients with chronic NP. Low certainty of evidence (GRADE ⊕⊕◯◯).

Important outcomes for decision-making

Health related quality of life and medication use

No study reported on the effect of rTMS on HRQoL or on pain relieving medication.

Complications

No serious or life threatening adverse events were observed when rTMS was used. The reported side effects mainly included mild headaches and an uncomfortable sensation of the magnetic pulse.

The accuracy of repetitive transcranial magnetic stimulation to predict the response of epidural motor cortex stimulation (PICO 2)

(Appendix 4:5, Appendix 4:6)

Three cross-sectional studies reported the effects of both rTMS followed by MCS in the same patients with data that could be used to calculate sensitivity and specificity of rTMS to predict a good response to MCS. There were some study limitations since only two of the studies had a blinded assessment of the outcome. There was also some uncertainty with regard to directness since the selection of patients was not adequately described. Due to small sample sizes in two studies there was also uncertainty with regard to precision.
The specificity of rTMS to predict a good clinical response was 75 % and 71 %, respectively, in the two studies that defined a good response as a reduction in the pain score of more than 30 %. It was 100 % in the study that defined a good response as over 50 % pain reduction. The corresponding sensitivity was 60 %, 74 % and 89 %. The positive predictive value was 90 %, 79 % and 100 %.
Conclusion: The response to rTMS may be a useful predictor of the response to MCS in patients with chronic NP. Low certainty of evidence (GRADE ⊕⊕◯◯).

9. Ethical issues (Appendix 5)

Repetitive TMS and epidural MCS are neuromodulation interventions that comply well with most ethical demands (see Appendix 5). They are not likely to cause serious complications. They make it possible to treat patients who are resistant to other treatments, and the pain reduction will probably improve their autonomy and quality of life. However, not all clinics have access to these therapies. Therefore, not all patients that may benefit from this intervention may be offered the treatment potentially leading to in inequity in healthcare. An introduction of both rTMS and MCS in the clinical routine will require extra resources with regard to personnel and laboratory and operating rooms. This will most probably have consequences for other patient groups in terms of growing waiting lists and treatment delay.

10. Organisational aspects

Time frame for the putative introduction of repetitive transcranial magnetic stimulation and epidural motor cortex stimulation

Both rTMS and MCS for treatment of chronic pain are already used at Sahlgrenska University Hospital (see under section 5 above). The equipment for rTMS is available at the Department of Clinical Neurophysiology.

Availability in other hospitals in Region Västra Götaland

Sahlgrenska University Hospital is the only hospital in Sweden in which rTMS is used for pain treatment purposes. Repetitive TMS is used for treatment of depression both in region Västra Götaland (Psykiatri Sydväst) and in Stockholm (Norra Stockholms Psykiatri). An HTA-report from the Swedish Council on Health Technology Assessment in Health Care on its use on this indication was published in 2009 (nr.192 published 2009-03-25).

Consequences for personnel

Currently, there are trained personnel (physician, biomedical analyst) available for handling and maintenance of the rTMS equipment at the Department of Clinical Neurophysiology, Sahlgrenska University Hospital, who can perform rTMS for screening of suitability for MCS. If rTMS also should be implemented on a regular and extended basis also for multiple session therapy additional personnel will be needed. This will require further education and training of more personnel.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

Patients for rTMS are mainly referred from neurology, rehabilitation and pain units where patients with chronic NP pose a considerable burden in terms of resources and health care costs. Present capacity at Sahlgrenska University Hospital for rTMS screening, as described above, is 10-20 patients on an annual basis.

11.Economic aspects

Present costs of implantation of neuromodulation devices

No recent calculations of the total costs for invasive neuromodulation procedures are available. The reimbursement per patient with chronic NP (ICD-10: M54, G54-59; I69) who is treated with surgical implantation or replacement of neuromodulation devices (surgical code KKÅ97: AAA30, AAA40, ABD60, ABD65, AEA00) is 166 000 SEK according to NordDRG 2017 (DRG A20N).

In 2015 and 2016, 40 and 60 patients, respectively, were implanted with neuromodulation devices for treatment of chronic NP at the Department of Neurosurgery, Sahlgrenska University Hospital. Thus, based on DRG A20N the total reimbursement for 2015 and 2016 were estimated to about 6 - 7 million and 9-10 million SEK, respectively.

All the 100 patients, with the exception of three, were treated with SCS. One third of them had a pulse generator (battery) replacement at an average material cost of 90 000 SEK. In most cases the pulse generator needs to be replaced every fourth to fifth year. Rechargeable pulse generators (device cost 90 000-150 000 SEK) should be considered when battery longevity is likely to be shorter, i.e. less than four years (Taylor et al., 2010). The longevity of rechargeable pulse generators is more than nine years.

Expected costs of repetitive transcranial magnetic stimulation

The equipment for rTMS (transcranial magnetic stimulator, NBS System 4.3, Nexstim, Helsinki, Finland, cost 900 000 SEK) is presently already available in the Department of Clinical Neurophysiology, Sahlgrenska University Hospital. It is used on a regular basis as a preoperative mapping tool in neurosurgical tumor surgery and for screening of suitability of invasive MCS in treatment of NP. The annual cost for service of the rTMS equipment according to the current service agreement between the Department of Clinical Neurophysiology and the producer Nexstim is 270 000 SEK. According to the producer, the coil has to be replaced every third year at a cost of 200 000 SEK. The cost for two rTMS sessions, i.e. active and sham stimulation, in the selection process for MCS suitability in management of chronic NP, is 46 000 SEK per patient as estimated by the Department of Clinical Neurophysiology.

Total change in cost

During the last few years three to four patients with chronic NP resistant to other therapies have been screened each year with rTMS. With an increase up to 15 patients the annual costs for rTMS screening would increase to approximately 700 000 SEK. Based on Nord DRG the additional cost for subsequent surgical implantation of a MCS system in each patient who has responded positively to rTMS is 166 000 SEK (see above). Accordingly, if 10 patients will have an implantation of a MCS system the additional annual cost is estimated to be 1.66 million SEK.

Possibility to adopt and use repetitive transcranial magnetic stimulation for screening within the present budget

The pilot study on rTMS as a selection tool for suitability of MCS that has been performed at Sahlgrenska University Hospital (10 patients) in a collaboration between the Departments of Neurosurgery and Clinical Neurophysiology was funded by research grants for the rTMS screening. Any funding for a continuation of this screening procedure is not included within the budget for 2017. Thus, additional funding will be needed to fully implement rTMS in the management of chronic NP (see above).

Available economic evaluations or cost advantages/disadvantages

All interventional neuromodulation techniques are associated with high initial material costs (80 000-200 000 SEK). There are no available health economic analyses on the cost-effectiveness of rTMS or MCS in management of chronic pain. Published systematic reviews and analyses that have evaluated the cost-effectiveness of SCS for patients with chronic post-surgical pain after spinal surgery have shown that SCS is less costly than other treatment alternatives in the long term (Simpson et al., 2009; Taylor et al., 2010). In a Canadian study it was shown that the mean cumulative cost for SCS therapy during a 5-year period was CAD 29 123 per patient (about 200 000 SEK) compared to CAD 38 029 (about 250 000 SEK) for conventional pain therapy (Kumar et al., 2002). The cost of treatment for the SCS group was greater than for the control group in the first 2.5 years due to the initial high costs of the implantable devices but became less than that for conventional pain therapy after this time, and remained so during the rest of the 5-year follow-up. The higher costs in the non-stimulator group were due medications, emergency center visits, x-rays, and ongoing physician visits and hospital admissions. In addition, 15 % of SCS-treated patients were able to return to work versus no patient in the control group.

12.Discussion

Neuromodulation techniques are most likely underused in the treatment of NP resistant to conventional non-invasive therapies. This is probably due to lack of awareness and knowledge among physicians about neuromodulation for NP, their high costs, and the shortage of high quality RCTs to motivate their use.

The present HTA analysis shows that rTMS may result in a reduction of NP compared to sham stimulation. The magnitude of pain reduction is modest and does not usually exceed 30 %, which is the criteria for clinically relevant reduction of pain (Farrar et al., 2001; Ostello et al., 2008). Multiple sessions of rTMS give better and more longstanding pain relief than single-session rTMS, and should be preferred when using this technique for pain treatment. Importantly, no serious or life threatening adverse events have been reported in association with this technique.

A single test session with rTMS also seems to be a reasonably good predictor of the response to epidural MCS. However, since the data is limited and based only on a small number of patients additional controlled clinical trials are needed to strengthen the validity of this tentative conclusion.

There is still a lack of knowledge of the effects of rTMS and MCS on HRQoL and ADL. To achieve an overall better completeness and stronger applicability of evidence these important outcome variables need to be addressed in future studies.

The conclusions of the present HTA report are in agreement with previous systematic reviews on the use of rTMS in pain treatment. In a Cochrane review from 2014 the authors concluded that there is a need for larger, rigorously designed studies, particularly of longer courses of stimulation (O'Connell et al. 2014). Since this review, several new and well-designed studies have been published which strengthen the evidence for a positive effect of rTMS, as observed in the present HTA-analysis. Our conclusions are similar with those in a recent publication that presents the current EAN guidelines on central neurostimulation therapy in chronic pain conditions (Cruccu et al., 2016). These guidelines state that a significant pain reduction as a response to a preoperative non-invasive rTMS test increases the probability of a good MCS therapeutic result, whilst lack of a good response to rTMS decreases it. This is further supported by the analysis of this HTA-report.

Chronic pain in general, and NP in particular, pose considerable burden in terms of health care resources and costs. The treatment options for NP when medication fails have been very limited. Neuromodulation strategies for treating chronic NP are rapidly developing. Based on the present HTA rTMS should most likely be used primarily as a test method to adequately select patients suitable for MCS. In parallel with the implementation of a new technology it is important to continue systematic follow up and evaluation of patient benefits and risks.

13.Future perspective

Scientific knowledge gaps

Although both invasive and non-invasive neuromodulation techniques have been applied for the treatment of NP for several years, there are still substantial knowledge gaps. There are insufficient data about the levels of effect in terms of both pain reduction and changes in HRQoL and ADL. Optimal stimulation techniques have to be elucidated more extensively and predictive factors for the efficacy of the different techniques in different types of NP should be defined in more detail. Furthermore, better data on health economics for these treatment modalities are needed.

Ongoing research

A search in Clinicaltrials.gov (2016-09-29) identified 229 trials. After evaluation by titles and data given in the database, six of these were deemed to be potentially relevant for the present issue, see table. Six RCTs are conducted in patients with different types and aetiologies of NP. The trials are designed to evaluate the effect of rTMS of motor cortex upon the perception of pain as evaluated by traditional pain assessment inventories (PICO 1).
No ongoing studies have been encountered focusing on the feasibility of rTMS in the selection of patients suitable for chronic MCS with implanted electrodes (PICO 2).

NCT nr	Country	Study design	Number Pts	Intervention	Primary outcome	Primary completion date
NCT02059096	France	RCT	66	rTMS	Change in level of pain	October 2016
NCT02277912	Finland	RCT	20	rTMS	Change in level of pain	March 2015
NCT02386969	France	RCT	50	rTMS	Change in level of pain	March 2018
NCT01746355	Brazil	RCT	40	rTMS	Change in level of pain	December 2012
NCT02010281	France	RCT, multicenter	230	rTMS	Change in level of pain	November 2017
NCT02030626	France	RCT	35	rTMS and tDCS	Change in level of pain	January 2015

14.Participants in the project

The question was nominated by

Goran Delic, Head of the Department of Neurology, Sahlgrenska University Hospital, Göteborg, Sweden.

Participating health care professionals

Kliment Gatzinsky, MD, PhD
Hans Silander, MD, Associate professor
Jennifer Samuelsson, MD
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Participants from the HTA-centrum

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Ann Liljegren, librarian
Ola Samuelsson, MD, Associate professor
Therese Svanberg, HTA librarian

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Declaration of interest

No one of the authors has any conflict of interest to declare.

Project time

HTA was accomplished during the period of 2015-12-07 – 2017-01-25
Literature searches were updated in June 2016.

Appendix 1, Search strategy, study selection and references

Questions at issue:
Does rTMS relieve pain better than placebo (sham treatment) in patients with chronic neuropathic pain, and can the response to rTMS predict the effect of MCS in these patients?

PICO 1 P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Patients with therapy-resistant NP originating from lesions in the central or peripheral nervous systems
I	Active rTMS targeting the primary motor cortex
C	Sham/placebo treatment
O	Critical for decision making Pain relief assessed by validated scales Important for decision making HRQoL according to validated scales Medication use Complications and adverse effects

PICO 2 P= Patients, I= Index test, C= Comparison/Reference test, O=Outcome

P	Patients with therapy-resistant NP originating from lesions in the central or peripheral nervous systems
I	Response to rTMS (clinically relevant pain reduction: yes/no)
C	Response to epidural MCS (clinically relevant pain reduction: yes/no)
O	Critical for decision making Sensitivity and specificity* Important for decision making Positive and negative prediction value of rTMS for MCS in pain treatment*

*Based on a clinically relevant pain reduction defined as a reduction of more than 30 %. The severity of pain was estimated by validated scales.

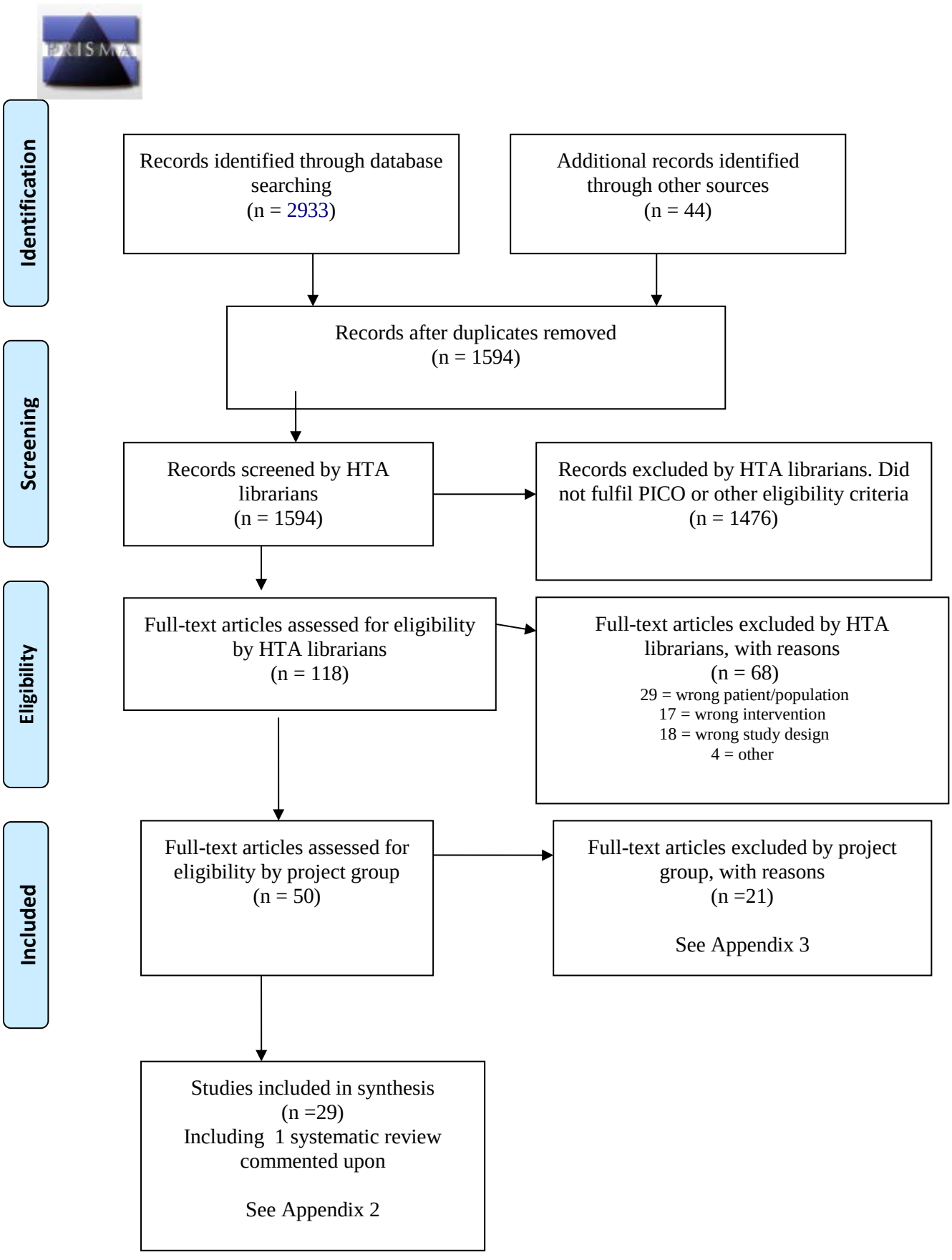
Eligibility criteria

Study design:
Systematic reviews
Randomized controlled trials
Non-randomized controlled studies
Case series etc. if ≥ 10 patients

Language:
English, French, Swedish, Norwegian, Danish

Publication date: 1990-

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 2015-12-15
No of results: 826
Search updated: 2016-06-08, 111 results

Search	Query	Result
#33	**Search #21 NOT #25 Filters: Publication date from 1990/01/01; Swedish; Norwegian; French; English; Danish**	**826**
#32	Search #21 NOT #25 Filters: Publication date from 1990/01/01; Swedish; Norwegian; French; English	826
#27	Search #21 NOT #25 Filters: Publication date from 1990/01/01	861
#26	Search #21 NOT #25	862
#25	Search #22 OR #23 OR #24	5744748
#24	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1443633
#23	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	4156670
#22	Search animals[ti] OR animal[ti] OR rats[ti] OR rat[ti] OR mouse[ti] OR mice[ti]	1270805
#21	Search #12 AND #20	941
#20	Search #18 OR #19	598539
#19	Search pain[tiab]	456174
#18	Search "Pain"[Mesh] OR "Pain Management"[Mesh]	330047
#12	Search #10 OR #11	13299
#11	Search transcranial magnet stimulation[tiab] OR transcranial magnetic stimulation[tiab] OR direct current stimulation[tiab] OR direct cortical stimulation[tiab] OR motor cortex stimulation[tiab]	12050
#10	Search "Transcranial Direct Current Stimulation"[Mesh] OR "Transcranial Magnetic Stimulation"[Mesh]	7844

Database: EMBASE (OVID SP)
Date: 2015-01-15
No of results: 989
Search updated: 2016-06-08, 170 results

Search	Query	Result
1	exp transcranial direct current stimulation/ or exp transcranial magnetic stimulation/	17952
2	(transcranial magnet stimulation or transcranial magnetic stimulation or direct current stimulation or direct cortical stimulation or motor cortex stimulation).ti,ab.	16116
3	1 or 2	20215
4	pain.ti,ab.	637833
5	pain/ or allodynia/ or chronic pain/ or intractable pain/ or neuralgia/ or phantom pain/ or psychogenic pain/ or referred pain/ or spinal pain/	286020
6	4 or 5	713656
7	3 and 6	1620
8	(animal not (animal and human)).sh.	1283602

9	(animals or animal or rats or rat or mouse or mice).ti.	1460232
10	8 or 9	2515827
11	7 not 10	1582
12	**limit 11 to (embase and (danish or english or french or norwegian or swedish) and yr="1990 -Current" and (article or conference paper or note or "review"))**	989

Database: The Cochrane Library
Date: 2015-01-15
No of results: 320
Cochrane reviews 5
Other reviews 6
Technology assessments 3
Clinical trials 306
Search updated: 2016-06-08, 69 results
Cochrane reviews 1
Clinical trials 68

Search	Query	Result
#1	transcranial magnet stimulation or transcranial magnetic stimulation or direct current stimulation or direct cortical stimulation or motor cortex stimulation:ti,ab,kw (Word variations have been searched)	2772
#2	MeSH descriptor: [Transcranial Magnetic Stimulation] explode all trees	857
#3	MeSH descriptor: [Transcranial Direct Current Stimulation] explode all trees	11
#4	#1 or #2 or #3	2772
#5	MeSH descriptor: [Pain] explode all trees	33829
#6	MeSH descriptor: [Pain Management] explode all trees	1737
#7	pain:ti,ab,kw (Word variations have been searched)	83792
#8	#5 or #6 or #7	89797
#9	**#4 and #8**	**320**

Database: PsycInfo (EBSCO)
Date: 2015-01-15
No of results: 427
Search updated: 2016-06-08, 21 results

Search	Query	Result
S10	**S7 NOT S8** Avgränsare - Publikationsdatum: 19900101-20151231; Språk: Danish, English, French, Norwegian, Swedish; Dokumenttyp: Journal Article, Review-Any; Exkludera doktorsavhandlingar	**427**
S9	S7 NOT S8	523
S8	TI animals OR animal OR rats OR rat OR mouse OR mice	111,166
S7	S3 AND S6	553

S6	S4 OR S5	75,142
S5	DE "Pain" OR DE "Chronic Pain" OR DE "Myofascial Pain" OR DE "Neuralgia" OR DE "Neuropathic Pain"	32,578
S4	TI pain OR AB pain	73,650
S3	S1 OR S2	9,807
S2	TI (transcranial magnet stimulation OR transcranial magnetic stimulation OR direct current stimulation OR direct cortical stimulation OR motor cortex stimulation) OR AB (transcranial magnet stimulation OR transcranial magnetic stimulation OR direct current stimulation OR direct cortical stimulation OR motor cortex stimulation)	9,339
S1	DE "Transcranial Magnetic Stimulation"	5,617

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited
2015-12-15
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 44 new records

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Appendix 2:1 – Characteristics of included studies. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1).

Author, Year, Country	Study Design	Follow-up after last stimulation	Site of stimulation	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men (%)	Outcome variables
Ahmed 2011 Egypt	Quasi-randomized	2 months	M1	rTMS (5 sessions -20 Hz) Sham (5 sessions)	n=17 n=10	52 53	77 60	Pain – VAS – LANS score - Endorphin
André-Obadia 2006 France	RCT Cross-over Double-blind	1 week	M1	rTMS (1 session-1 Hz) rTMS (1 session-20 Hz) Sham (1 session)	n=14	53	71	Pain – VAS – Global subjective assessment
André-Obadia 2008 France	RCT Cross-over Double-blind	2 weeks	M1	rTMS (1 session-20 Hz) Sham (1 session)	n=30	55	77	Pain – VAS
André-Obadia 2011 France	RCT Cross-over Double-blind	2 weeks	M1	rTMS (1 session-20 Hz) Sham (1 session)	n=45	55	62	Pain – VAS
Attal 2016 France	RCT Parallel groups Double-blind	5 weeks	M1	rTMS (3 sessions-10 Hz) Sham (3 sessions)	n=24 n=12	52	51	Pain – BPI scale - NPSI

Abbreviations: M1 = primary motor cortex; rTMS = repetitive Transcranial Magnetic Stimulation; VAS = Visual Analogous Scale; LANSS= Leeds Assessment of neuropathic Sympto.ms and Signs, , BPI = Brief Pain Inventory , NRS = Numeric Rating Scale (0 = no pain, 10 = worst possible pain), VDS = Verbal Description Scale, TOTPAR = Total Pain Relief, NR = Not reported.

Appendix 2:1 – Characteristics of included studies. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1).

Author, Year, Country	Study Design	Follow-up after last stimulation	Site of stimulation	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men (%)	Outcome variables
Defrin Israeel 2007	RCT Parallel groups Double-blind	10 days	M1	rTMS (10 sessions-5 Hz) Sham (10 sessions)	n=6 n=6	54	63	Pain – VAS scale - SF-MPQ
Hirayama Japan 2006	RCT Cross-over Double-blind	3 hours	M1	rTMS (1 session - 5 Hz) Sham (1 session)	n=20	57	65	Pain – VAS – SF-MPQ
Hosomi Japan 2013b	RCT Cross-over Double-blind	29 days	M1	rTMS (10 sessions-Hz) Sham (10 sessions)	n=70	61	62	Pain – VAS – SF-MPQ
Jette 2013 Canada	RCT Cross-over Double-blind	5-6 days	M1	rTMS (1 session-10 Hz hand) rTMS (1 session-leg) Sham (1 session)	n=16	50	69	Pain – NRS
Kang 2009 South Korea	RCT Cross-over Double-blind	7 weeks	M1	rTMS (1 session-10 Hz) Sham (1 session)	n=13	55	55	Pain – NRS - BPI

Abbreviations: M1 = primary motor cortex; rTMS = repetitive Transcranial Magnetic Stimulation; VAS = Visual Analogous Scale; LANSS= Leeds Assessment of neuropathic Sympto.ms and Signs, , BPI = Brief Pain Inventory , NRS = Numeric Rating Scale (0 = no pain, 10 = worst possible pain), VDS = Verbal Description Scale, TOTPAR = Total Pain Relief, NR = Not reported.

Appendix 2:1 – Characteristics of included studies. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1).

Author, Year, Country	Study Design	Follow-up after last stimulation	Site of stimulation	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men (%)	Outcome variables
Khedr 2015 Egypt	RCT Parallel groups Double-blind	1 month	M1	rTMS (10 sessions-20 Hz) Sham (10 sessions)	n=17 n=17	48	10	Pain – VAS -VDS -LANSS -HAM-D
Lefaucheur 2001a France	RCT Cross-over Double-blind	3 weeks	M1	rTMS (1 session-10 Hz) rTMS (1 session-0,5 Hz) Sham (1 session)	n=18	55	61	Pain – VAS scale
Lefaucheur 2001b France	RCT Cross-over Double-blind	12 days	M1	rTMS (1 session-10 Hz) Sham (1 session)	n=14	57	43	Pain – VAS scale
Lefaucheur 2004	RCT Cross-over Double-blind	5 minutes	M1	rTMS (1 session-10 Hz) Sham (1 session	n=60	NR	NR	Pain – VAS scale

Abbreviations: M1 = primary motor cortex; rTMS = repetitive Transcranial Magnetic Stimulation; VAS = Visual Analogous Scale; LANSS= Leeds Assessment of neuropathic Sympto.ms and Signs, , BPI = Brief Pain Inventory , NRS = Numeric Rating Scale (0 = no pain, 10 = worst possible pain), VDS = Verbal Description Scale, TOTPAR = Total Pain Relief, NR = Not reported.

Appendix 2:1 – Characteristics of included studies. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1).

Author, Year, Country	Study Design	Follow-up after last stimulation	Site of stimulation	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men (%)	Outcome variables
Lefaucheur 2008 France	RCT Cross-over Double-blind	3 weeks	M1	rTMS (1 session- 10 Hz) rTMS (1 session- 1 Hz) Sham (1 session)	n=48	54	50	Pain – VAS scale
Malavera 2016 Colombia	RCT Parallel groups Double-blind	30 days	M1	rTMS (10 sessions- 10 Hz) Sham (10 sessions)	n=54	34	9	Pain – VAS scale
Nurmikko 2016 UK	RCT Cross-over Double-blind	3 weeks	M1	rTMS (5 sessions- 10 Hz) Sham (5 sessions)	n=40	53	57	Pain – NRS
Picarreli 2010 Brazil	RCT Parallel groups Double-blind	3 months	M1	rTMS (10 sessions - 10 Hz) Sham (10 sessions)	n=12 n=11	42	31	Pain – VAS - SF-MPQ
Pleger 2004 Germany	RCT Cross-over Double-blind	90 minutes	M1	rTMS (1 session- 10 Hz) Sham (1 session)	n=10	51	30	Pain – VAS

Abbreviations: M1 = primary motor cortex; rTMS = repetitive Transcranial Magnetic Stimulation; VAS = Visual Analogous Scale; LANSS= Leeds Assessment of neuropathic Sympto.ms and Signs, , BPI = Brief Pain Inventory , NRS = Numeric Rating Scale (0 = no pain, 10 = worst possible pain), VDS = Verbal Description Scale, TOTPAR = Total Pain Relief, NR = Not reported.

Appendix 2:1 – Characteristics of included studies. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1).

Author, Year, Country	Study Design	Follow-up after last stimulation	Site of stimulation	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men (%)	Outcome variables
Saitoh 2007 Japan	RCT Cross-over Double-blind	180 minutes	M1	rTMS (1 session-10 Hz) rTMS (1 session-5 Hz) rTMS (1 session-1 Hz) Sham (1 session)	n=13	59	54	Pain – VAS - SF-MPQ
Yilmaz 2014 Turkey	RCT Parallel groups Double-blind	6 months	M1	rTMS (10 sessions - 10 Hz) Sham (10 sessions)	n=9 n=7	39	100	Pain – VAS scale
Kobayashi 2015 Japan	Case series	12 weeks	M1	rTMS (12 sessions - 5 Hz)	n=20	63	60	Pain – VAS scale
Lefaucheur 2006 France	Case series	1 week	M1	rTMS (2 sessions - 10 Hz)	n=36	53	39	Pain – VAS scale
Lefaucheur 2012 France	Case series	4 weeks	M1	rTMS (2 sessions - 10 Hz)	n=14	54	64	Pain – VAS scale

Abbreviations: M1 = primary motor cortex; rTMS = repetitive Transcranial Magnetic Stimulation; VAS = Visual Analogous Scale; LANSS= Leeds Assessment of neuropathic Sympto.ms and Signs, , BPI = Brief Pain Inventory , NRS = Numeric Rating Scale (0 = no pain, 10 = worst possible pain), VDS = Verbal Description Scale, TOTPAR = Total Pain Relief, NR = Not reported.

Appendix 2:2 – Characteristics of included studies. Motor cortex stimulation in patients with chronic neuropathic pain. PICO 2.

Author, Year, Country	Study Design	Follow-up	Site of stimu-lation	Intervention	Patients (n)	Mean Age (years)	Men (%)	Outcome variables
André-Obadia 2014 France	Cross-sectional study	Mean: 6.1 years	M1	rTMS and shamTMS in all patients prior to MCS. MCS in all patients	n=20	54	55	Pain – VAS – CPA
Hosomi 2008 Japan	Cross-sectional study	Mean: 4.2 years (range 1.1–9.3)	M1	rTMS in 11 patients prior to MCS. MCS in all patients	n=34	57	82	Pain – VAS
Lefaucher 2011 France	Cross-sectional study	> 1 year	M1	rTMS and shamTMS in all patients prior to MCS. MCS in all patients	n=59	55	59	Pain – VAS
Mandat 2012 Poland	Cross-sectional study	3 months	M1	rTMS in 16 patients prior to MCS. MCS in all patients	n=23	53	48	Pain – VAS

Abbreviations: M1 = primary motor cortex; rTMS = repetitive Transcranial Magnetic Stimulation; VAS = Visual Analogous Scale, CPA =Combined Pain Assessment Score.

Appendix 3. Excluded articles

Study (author, publication year)	Reason for exclusion
Brown et al, 2005	Not the specified intervention
Boldt et al, 2014	Systematic review
De Oliveira et al, 2014	Not the specified intervention
El-Habashy et al, 2013	Case series, Adverse events not reported
Fricova et al, 2013	Not the specified patient category; mixed patient group
Galhardoni et al, 2015	Systematic review
Goto et al, 2008	Not the specified outcome variables
Hasan et al, 2014	Case series, Adverse events not reported
Hodaj et al, 2015	Not the specified patient category; mixed patient group
Hosomi et al, 2013a	Case series, Adverse events not reported
Jin et al, 2015	Systematic review
Khedr et al, 2005	Not the specified patient category, Not the specified outcome variables
Lefaucher et al, 2010	Not the specified intervention
Leung et al, 2009	Systematic review
Lindholm et al, 2016	Not the specified intervention
Matsumura et al, 2013	Case series, Adverse events not reported
Ohn et al, 2012	Case series, Adverse events not reported
Onesti et al, 2013	Not the specified intervention
Rollnik et al, 2002	Not the specified patient category; mixed patient group
Saitoh et al, 2006	Case series, Adverse events not reported
Saitoh et al, 2013	Case series. Duplicate publication; Hosomi 2008.

* + No or minor problems
? Some problems
- Major problems

Appendix 4:1: Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Ahmed 2011 Egypt	Quasi-randomized	27 17 rTMS 10 sham	0	<u>VAS</u> Baseline: 7.4 (sd 1.3) After 5 sessions: 3.4 (sd 1.2) After 2 months: 4.5 (sd 2.2) <u>LANS</u> Baseline: 17.2 (sd 3.7) After 5 sessions: 8.4 (sd 3.7) After 2 months: 9.5 (sd 3.7) p = 0.01 between study groups for both VAS and LANS	<u>VAS</u> Baseline: 7.6 (sd 0.8) After 5 sessions: 7.4 (sd 0.8) After 2 months: 7.6 (sd 1.0) <u>LANS</u> Baseline: 18.1 (sd 1.9) After 5 sessions: 17.8 (sd 2.3) After 2 months: 16.8 (sd 1.7)	All patients had phantom pain after amputation. No statistical inference tests were performed between study groups.	+/?	?	?
André-Obadia 2006 France	RCT Cross-over Double-blind	14	2	<u>VAS</u> After 1 week: - 11 % No difference between treatments	<u>VAS</u> After 1 week: - 8 %	Type of patients: 10 post-stroke, 1 spinal cord injury, 3 peripheral lesion. Only rTMS with 20 Hz is presented in this appendix	?	+	?
André-Obadia 2008 France	RCT Cross-over Double-blind	30	2	<u>VAS</u> After 5 days: rTMS 7 % (15%) lower compared to sham* p = 0.03 between treatments		Type of patients: 14 post-stroke, 4 spinal cord injury, 7 peripheral lesion, 5 trigeminus neuralgia. All 14 patients in the study published 2006 are included in this analysis. *estimated from Figure 3	?	+	?

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:1: Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
André-Obadia 2011 France	RCT Cross-over Double-blind	45	0	VAS After 5 days: - 9.6 % p < 0.001 between treatments	VAS After days: - 0.6 %	Placebo effect when following a successful active rTMS. Small clinical effect.	?	-	?
Attal 2016 France	RCT Parallel groups Double-blind	51	16	BPI Baseline: 5.9* After 5 days: 4.5* p < 0.05 between study groups NPSI total Baseline: 35.3 (sd12.6) After 5 days: 24.0 (sd17.4) p = 0.04 between study groups	BPI Baseline: 6.2* After 5 days: 6.0* NPSI total Baseline: 34.2 (sd 20.4) After 5 days: 31.9 (sd 21.8)	All patients had neuropathic pain due lumbosacral radiculopathy. *estimated from Figure 3	+	+	+

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:1: Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Defrin 2007 Israel	RCT Parallel groups Double-blind	12	1	VAS Baseline: 4.6* After10 sessions: 3.3* No difference between treatments	VAS Baseline: 3.4* After10 sessions: 1.5*	Type of patients: 12 spinal cord injury	?	?	?
Hirayama 2006 Japan	RCT Cross-over Double-blind	20		VAS Baseline: 8.2* After1 session: 7.7* No difference between treatments	VAS Baseline: 8.1* After1 session: 8.2* .	Type of patients: 12 post-stroke pain, 2 spinal cord lesion, 3 trigeminal neuralgia, 1 brachial plexus injury, 1 cauda equina lesion.	?	-	-
Hosomi 2013b Japan	RCT Cross-over Double-blind	70	9	VAS After 10 sessions: - 3.4 % (95 % CI: -1.1; -5.6 %)	VAS After 10 sessions: +0.7 % (95 % CI: +2.7;–1.4)	Type of patients: 52 post-stroke pain, 7 spinal cord lesion, 3 phantom pain, 2 peripheral lesion.	?	+	+
Jette 2013 Canada	RCT Cross-over Double-blind	18	2	NRS After 5-6 days: - 5.1 %* No difference between treatments	NRS After 5-6 days: - 4.9* %	All patients had spinal cord injury (complete or incomplete). *estimated from Figure 1 B	?	-	?

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:1: Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Kang 2009 South Korea	RCT Cross-over Double-blind	13	2	NRS Baseline: 6.5 (sd 2.2) After 1 week: 5.5 (sd 1.8) After 7 weeks: 5.7 (sd 2.1) No difference between treatments	NRS Baseline: 6.1 (sd 1.8) After 1 week: 5.9 (sd 2.0) After 7 weeks: 5.9 (sd 2.1)	All patients had spinal cord injury (complete or incomplete). NRS data are NRS for average pain	+	?	?
Khedr 2014 Egypt	RCT Parallel groups Double-blind	34	4	VAS Baseline: 6.3 (sd 0.5) After 15 days: 4.0* After 1 month: 4.8* p = 0.014 after 15 days and no difference at 1 month between treatments	VAS Baseline: 6.1 (sd 0.6) After 15 days: 5.0* After 1 month: 5.1*	Type of patients: 29 post-mastectomy neuropathic pain, 5 other soft tissue tumor neuropathic pain. *estimated from Figure 2	?	+	+
Lefaucheur 2001a France	RCT Cross-over Double-blind	18	0	VAS Baseline: 7.0 (sd 0.4) After 1 session: 5.6 (sd 0.6) p < 0.05 between treatments	VAS Baseline: 6.7 (sd 0.5) After 1 session: 6.2 (sd 0.5)	Type of patients: 6 post-stroke, 6 brain stem lesion, 6 brachial plexus lesion.	?	-	-

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:1: Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Lefaucheur 2001b France	RCT Cross-over	14	0	VAS Baseline: 6.7* After 1 week: 5.5* After 12 days: 6.7* p< 0.05 after 1 weeks and no difference after 12 days between treatments	VAS Baseline: 6.4* After 1 week: 7.8* After 12 days: 8.5* .	Type of patients: 7 post-stroke, 7 trigeminal neuralgia. *estimated from Figure 1a	?	?	?
Lefaucheur 2004 France	RCT Cross-over Double-blind	60	0	VAS Baseline: 6.8 (sd 0.2) After 1 session: 5.0 (sd 0.4) p< 0.001 between treatments	VAS Baseline: 6.8 (sd 0.2) After 1 session: 5.8 (sd 0.3)	Type of patients: 24 post-stroke, 12 trigeminal neuralgia, 12 brachial plexus lesion, 12 spinal cord lesion.			
Lefaucheur 2008 France	RCT Cross-over Double-blind	48	2	VAS Baseline: 6.6 (sd 0.3) After 1 session: 5.4 (sd 0.3) p< 0.05 between treatments	VAS Baseline: 6.4(sd 0.3) After 1 session: 6.2 (sd 0.3)	Type of patients: 13 post-stroke, 13 trigeminal neuralgia, , 10 brachial plexus lesion, 10 spinal cord lesion.	?	?	?

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems ? Some problems - Major problems

Appendix 4:1: Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Malavera 2016 Colombia	RCT Parallel groups Double-blind	54		<u>VAS</u> Baseline: 4.9 (sd 1.8) After 15 days: 2.3 (sd 2.5) After 30 days: 3.0 (sd 2.6) p< 0.05 after 15 days and no difference after 30 days between treatments	<u>VAS</u> Baseline: 4.8 (sd 1.8) After 15 days: 3.7 (sd 3.0) After 30 days: 3.9 (sd 2.7)	All patients had phantom limb pain.	+	+	+
Nurmikko 2016 UK	RCT Cross-over Double-blind	40	13	<u>NRS</u> Baseline: 6.8 (sd 1.7) After 1 week: Δ -0.6 (sd 1.0) After 3 weeks: Δ -0.5 (sd 1.1) p < 0.05 at 1 and 3 weeks between treatments	<u>NRS</u> Baseline: 6.5 (sd 1.8) After 1 week: Δ -0.01(sd 0.8) After 3 weesk: Δ -0.2 (sd 0.9)	Type of patients: 2 post-stroke, 12 trigeminal neuralgia, , 4 brachial plexus lesion, 4 phantom pain, 4 peripheral nerve lesion, 2 spinal cord lesion, 12 other diagnoses.	?	-	?
Picarreli 2010 Brazil	RCT Parallel groups Double-blind	23	1	<u>VAS</u> Baseline: 9.3 (sd 0.9) After 1 week: 3.9 After 3 months: 8.0 p< 0.05 after 1 week between treatments	<u>VAS</u> Baseline: 8.8 (sd 1.0) After 1 week: 6.4 After 3 months: 6.9	All patients had complex regional pain syndrome. Etiology not specified			

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:1: Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Pleger 2004 Germany	RCT Cross-over Double-blind	10	0	VAS Baseline: 4.7 /sd 2.6) After 90 min: 3.7 (sd 2.9) p = 0.02 between treatments	VAS Baseline: 4.4* After 1 week: 4.5* .	Type of patients: Complex regional pain syndromeafter trauma, fracture or luxation. *estimated from Figure 1b	?	?	-
Saitoh 2007 Japan	RCT Cross-over Double-blind	13	0	VAS Change at 180 minutes: - 10 % p < 0.05 between treatments	VAS Change at 180 minutes: + 2 %	Type of patients: 7 post-stroke, 1 brachial plexus lesion, 1 phantom pain, 1 peripheral nerve lesion, 2 spinal cord lesion, 1 cauda equinea lesion. *estimated from Figure 1	-	-	-
Yilmaz 2014 Turkey	RCT Cross-over Double-blind	17	1	VAS Baseline: 7.0 After 10 days: 5.0 After 6 weeks: 5.0 After 6 months: 7.0 No difference at any time between treatments	VAS Baseline: 7.0 After 10 days: 6.0 After 6 weeks: 7.0 After 6 months: 7.0.	All patients had spinal cord injury (complete or incomplete). *estimated from Figure 1	?	?	?

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:2. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Trials of single session rTMS. Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
André-Obadia 2006 France	RCT Cross-over Double-blind	14	2	VAS After 1 week: - 11 % No difference between treatments	VAS After 1 week: - 8 %	Type of patients: 10 post-stroke, 1 spinal cord injury, 3 peripheral lesion. Only rTMS with 20 Hz is presented in this appendix	?	+	?
André-Obadia 2008 France	RCT Cross-over Double-blind	30	2	VAS After 5 days: rTMS 7 % (15%) lower compared to sham* p = 0.03 between treatments		Type of patients: 14 post-stroke, 4 spinal cord injury, 7 peripheral lesion, 5 trigeminus neuralgia. All 14 patients in the study published 2006 are included in this analysis. *estimated from Figure 3	?	+	?
André-Obadia 2011 France	RCT Cross-over Double-blind	45	0	VAS After 5 days: - 9.6 % p < 0.001 between treatments	VAS After days: - 0.6 %	Placebo effect when following a successful active rTMS. Small clinical effect.	?	-	?

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:2. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Trials of single session rTMS. Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Hirayama 2006 Japan	RCT Cross-over Double-blind	20		VAS Baseline: 8.2* After1 session: 7.7* Change after 1 session: -6% No difference between treatments	VAS Baseline: 8.1* After1 session: 8.2* Change after 1 session: +1% .	Type of patients: 12 post-stroke pain, 2 spinal cord lesion, 3 trigeminal neuralgia, 1 brachial plexus injury, 1 cauda □quine lesion.	?	-	-
Jette 2013 Canada	RCT Cross-over Double-blind	18	2	NRS After 5-6 days: - 5.1 %* No difference between treatments	NRS After 5-6 days: - 4.9* %	All patients had spinal cord injury (complete or incomplete). *estimated from Figure 1 B	?	-	?
Kang 2009 South Korea	RCT Cross-over Double-blind	13	2	NRS Baseline: 6.5 (sd 2.2) After 1 week: 5.5 (sd 1.8) After 7 weeks: 5.7 (sd 2.1) Change after 1 week: -15 % No difference between treatments	NRS Baseline: 6.1 (sd 1.8) After 1 week: 5.9 (sd 2.0) After 7 weeks: 5.9 (sd 2.1) Change after 1 week: -3 %	All patients had spinal cord injury (complete or incomplete). NRS data are NRS for average pain	+	?	?

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:2. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Trials of single session rTMS. Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Lefaucheur 2001a France	RCT Cross-over Double-blind	18	0	VAS Baseline: 7.0 (sd 0.4) After 1 session: 5.6 (sd 0.6) Change after 1 session: -20% p < 0.05 between treatments	VAS Baseline: 6.7 (sd 0.5) After 1 session: 6.2 (sd 0.5) Change after 1 session: -7%	Type of patients: 6 post-stroke, 6 brain stem lesion, 6 brachial plexus lesion.	?	-	-
Lefaucheur 2001b France	RCT Cross-over	14	0	VAS Baseline: 6.7* After 1 week: 5.5* After 12 days: 6.7* Change after 1 week: -18 % p< 0.05 between treatments	VAS Baseline: 6.4* After 1 week: 7.8* After 12 days: 8.5* Change after 1 week: +22 %	Type of patients: 7 post-stroke, 7 trigeminal neuralgia. *estimated from Figure 1a	?	?	?

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems ? Some problems - Major problems

Appendix 4:2. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Trials of single session rTMS. Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Lefaucheur 2004 France	RCT Cross-over Double-blind	60	0	VAS Baseline: 6.8 (sd 0.2) After 1 session: 5.0 (sd 0.4) Change after 1 session: -23% p< 0.001 between treatments	VAS Baseline: 6.8 (sd 0.2) After 1 session: 5.8 (sd 0.3) Change after 1 session: -8%	Type of patients: 24 post-stroke, 12 trigeminal neuralgia, 12 brachial plexus lesion, 12 spinal cord lesion.			
Lefaucheur 2008 France	RCT Cross-over Double-blind	48	2	VAS Baseline: 6.6 (sd 0.3) After 1 session: 5.0 (sd 0.4) Change after 1 session: -24% p< 0.05 between treatments	VAS Baseline: 6.4(sd 0.3) After 1 session: 5.8 (sd 0.3) Change after 1 session: -9%	Type of patients: 13 post-stroke, 13 trigeminal neuralgia, , 10 brachial plexus lesion, 10 spinal cord lesion.	?	?	?

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:2. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Trials of single session rTMS. Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Pleger 2004 Germany	RCT Cross-over Double-blind	10	0	VAS Baseline: 4.7 /sd 2.6) After 90 min: 3.7 (sd 2.9) Change after 1 session: -21% p = 0.02 between treatments	VAS Baseline: 4.4* After 1 week: 4.5* Change after 1 session: +2%	Type of patients: Complex regional pain syndromeafter trauma, fracture or luxation. *estimated from Figure 1b	?	?	-
Saitoh 2007 Japan	RCT Cross-over Double-blind	13	0	VAS Change at 180 minutes: - 10 % p < 0.05 between treatments	VAS Change at 180 minutes: + 2 %	Type of patients: 7 post-stroke, 1 brachial plexus lesion, 1 phantom pain, 1 peripheral nerve lesion, 2 spinal cord lesion, 1 cauda equinea lesion. *estimated from Figure 1	-	-	-

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:3: Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Trials of multiple session rTMS.Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Ahmed 2011 Egypt	Quasi-randomized	27 17 rTMS 10 sham	0	<u>VAS</u> Baseline: 7.4 (sd 1.3) After 5 sessions: 3.4 (sd 1.2) After 2 months: 4.5 (sd 2.2) <u>LANS</u> Baseline: 17.2 (sd 3.7) After 5 sessions: 8.4 (sd 3.7) After 2 months: 9.5 (sd 3.7) p = 0.01 between study groups for both VAS and LANS	<u>VAS</u> Baseline: 7.6 (sd 0.8) After 5 sessions: 7.4 (sd 0.8) After 2 months: 7.6 (sd 1.0) <u>LANS</u> Baseline: 18.1 (sd 1.9) After 5 sessions: 17.8 (sd 2.3) After 2 months: 16.8 (sd 1.7)	All patients had phantom pain after amputation. No statistical inference tests were performed between study groups.	+/?	?	?
Attal 2016 France	RCT Parallel groups Double-blind	51	16	<u>BPI</u> Baseline: 5.9* After 5 days: 4.5* p < 0.05 between study groups <u>NPSI total</u> Baseline: 35.3 (sd12.6) After 5 days: 24.0 (sd17.4) p = 0.04 between study groups	<u>BPI</u> Baseline: 6.2* After 5 days: 6.0* <u>NPSI total</u> Baseline: 34.2 (sd 20.4) After 5 days: 31.9 (sd 21.8)	All patients had neuropathic pain due lumbosacral radiculopathy. *estimated from Figure 3	+	+	+

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms) 1(4)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:3: Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Trials of multiple session rTMS.Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Defrin 2007 Israel	RCT Parallel groups Double-blind	12	1	VAS Baseline: 4.6* After10 sessions: 3.3* No difference between treatments	VAS Baseline: 3.4* After10 sessions: 1.5*	Type of patients: 12 spinal cord injury	?	?	?
Hosomi 2013b Japan	RCT Cross-over Double-blind	70	9	VAS After 10 sessions: - 3.4 % (95 % CI: -1.1; -5.6 %)	VAS After 10 sessions: +0.7 % (95 % CI: +2.7;–1.4)	Type of patients: 52 post-stroke pain, 7 spinal cord lesion, 3 phantom pain, 2 peripheral lesion.	?	+	+
Khedr 2014 Egypt	RCT Parallel groups Double-blind	34	4	VAS Baseline: 6.3 (sd 0.5) After 15 days: 4.0* After 1 month: 4.8* p = 0.014 after 15 days and no difference at 1 month between treatments	VAS Baseline: 6.1 (sd 0.6) After 15 days: 5.0* After 1 month: 5.1*	Type of patients: 29 post-mastectomy neuropathic pain, 5 other soft tissue tumor neuropathic pain. *estimated from Figure 2	?	+	+

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms) 2(4)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:3: Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Trials of multiple session rTMS.Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Malavera 2016 Colombia	RCT Parallel groups Double-blind	54		VAS Baseline: 4.9 (sd 1.8) After 15 days: 2.3 (sd 2.5) After 30 days: 3.0 (sd 2.6) p< 0.05 after 15 days and no difference after 30 days between treatments	VAS Baseline: 4.8 (sd 1.8) After 15 days: 3.7 (sd 3.0) After 30 days: 3.9 (sd 2.7)	All patients had phantom limb pain.	+	+	+
Nurmikko 2016 UK	RCT Cross-over Double-blind	40	13	NRS Baseline: 6.8 (sd 1.7) After 1 week: Δ -0.6 (sd 1.0) After 3 weeks: Δ -0.5 (sd 1.1) p < 0.05 at 1 and 3 weeks between treatments	NRS Baseline: 6.5 (sd 1.8) After 1 week: Δ -0.01(sd 0.8) After 3 weesk: Δ -0.2 (sd 0.9)	Type of patients: 2 post-stroke, 12 trigeminal neuralgia, , 4 brachial plexus lesion, 4 phantom pain, 4 peripheral nerve lesion, 2 spinal cord lesion, 12 other diagnoses.	?	-	?
Picarreli 2010 Brazil	RCT Parallel groups Double-blind	23	1	VAS Baseline: 9.3 (sd 0.9) After 1 week: 3.9 After 3 months: 8.0 p< 0.05 after 1 week between treatments	VAS Baseline: 8.8 (sd 1.0) After 1 week: 6.4 After 3 months: 6.9	All patients had complex regional pain syndrome. Etiology not specified			

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms) 3(4)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:3: Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1)
Trials of multiple session rTMS.Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Yilmaz 2014 Turkey	RCT Cross-over Double-blind	17	1	<u>VAS</u> Baseline: 7.0 After 10 days: 5.0 After 6 weeks: 5.0 After 6 months: 7.0 No difference at any time between treatments	<u>VAS</u> Baseline: 7.0 After 10 days: 6.0 After 6 weeks: 7.0 After 6 months: 7.0.	All patients had spinal cord injury (complete or incomplete). *estimated from Figure 1	?	?	?

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms) 4(4)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:4. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1).
Trials of multiple session rTMS. Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Ahmed 2011 Egypt	Quasi-randomized	27 17 rTMS 10 sham	0	VAS Baseline: 7.4 (sd 1.3) After 5 sessions: 3.4 (sd 1.2) After 2 months: 4.5 (sd 2.2) Change at 2 months: - 39 %	VAS Baseline: 7.6 (sd 0.8) After 5 sessions: 7.4 (sd 0.8) After 2 months: 7.6 (sd 1.0) Change at 2 months: ± 0 %	All patients had phantom pain after amputation. No statistical inference tests were performed between study groups.	+/?	?	?
Attal 2016 France	RCT Parallel groups Double-blind	51	16	BPI Baseline: 5.9* After 5 days: 4.5* Change at 5 days: - 24 %	BPI Baseline: 6.2* After 5 days: 6.0* Change at 5 days: - 3 %	All patients had neuropathic pain due lumbosacral radiculopathy. *estimated from Figure 3	+	+	+
Defrin 2007 Israel	RCT Parallel groups Double-blind	12	1	VAS Baseline: 4.6* After10 sessions: 3.3* Change after 10 sessions: - 28 %	VAS Baseline: 3.4* After10 sessions: 1.5* Change after 10 sessions: - 26 %	Type of patients: 12 spinal cord injury	?	?	?

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:4. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1).
Trials of multiple session rTMS. Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Hosomi 2013b Japan	RCT Cross-over Double-blind	70	9	VAS Change after 10 sessions: - 3.4 % (95 % CI: -1.1; -5.6 %)	VAS Change after 10 sessions: +0.7 % (95 % CI: +2.7;–1.4)	Type of patients: 52 post-stroke pain, 7 spinal cord lesion, 3 phantom pain, 2 peripheral lesion.	?	+	+
Khedr 2014 Egypt	RCT Parallel groups Double-blind	34	4	VAS Baseline: 6.3 (sd 0.5) After 15 days: 4.0* After 1 month: 4.8* Change at 1 month: -24 %	VAS Baseline: 6.1 (sd 0.6) After 15 days: 5.0* After 1 month: 5.1* Change at 1 month: -16 %	Type of patients: 29 post-mastectomy neuropathic pain, 5 other soft tissue tumor neuropathic pain. *estimated from Figure 2	?	+	+
Malavera 2016 Colombia	RCT Parallel groups Double-blind	54		VAS Baseline: 4.9 (sd 1.8) After 15 days: 2.3 (sd 2.5) After 30 days: 3.0 (sd 2.6) Change at 1 month: -39 %	VAS Baseline: 4.8 (sd 1.8) After 15 days: 3.7 (sd 3.0) After 30 days: 3.9 (sd 2.7) Change at 1 month: -19 %	All patients had phantom limb pain.	+	+	+

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:4. Real rTMS versus sham rTMS in patients with chronic neuropathic pain (PICO 1).
Trials of multiple session rTMS. Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				rTMS (5, 10 or 20 Hz)	Sham				
Nurmikko 2016 UK	RCT Cross-over Double-blind	40	13	NRS Baseline: 6.8 (sd 1.7) After 1 week: Δ -0.6 (sd 1.0) After 3 weeks: Δ -0.5 (sd 1.1) Change at 3 weeks: -7 %	NRS Baseline: 6.5 (sd 1.8) After 1 week: Δ -0.01(sd 0.8) After 3 weesk: Δ -0.2 (sd 0.9) Change at 3 weeks: -3 %	Type of patients: 2 post-stroke, 12 trigeminal neuralgia, , 4 brachial plexus lesion, 4 phantom pain, 4 peripheral nerve lesion, 2 spinal cord lesion, 12 other diagnoses.	?	-	?
Picarreli 2010 Brazil	RCT Parallel groups Double-blind	23	1	VAS Baseline: 9.3 (sd 0.9) After 1 week: 3.9 After 3 months: 8.0 Change at 1 week: -57 %	VAS Baseline: 8.8 (sd 1.0) After 1 week: 6.4 After 3 months: 6.9 Change at 1 week: -27 %	All patients had complex regional pain syndrome. Etiology not specified			
Yilmaz 2014 Turkey	RCT Cross-over Double-blind	17	1	VAS Baseline: 7.0 After 10 days: 5.0 After 6 weeks: 5.0 After 6 months: 7.0 Change at 6 weeks: -28 %	VAS Baseline: 7.0 After 10 days: 6.0 After 6 weeks: 7.0 After 6 months: 7.0. Change at 6 weeks: ± 0 %	All patients had spinal cord injury (complete or incomplete). *estimated from Figure 1	?	?	?

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale; LANS = ,
BPI = Brief Pain Inventory(0 = no pain, 10 = maximal pain), NPSI = Neuropathic Pain Symptom Inventory (0 = no symptoms, 100 = maximal symptoms) 3(3)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:5. Motor cortex stimulation in patients with chronic neuropathic pain. PICO 2
Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				MCS	Control group				
André-Obadia 2006 France	Case series Retrospective	14	3	VAS Baseline and follow-up data are NR	None	Type of patients: 10 post-stroke, 1 spinal cord injury, 3 peripheral lesion.			
		12							
André-Obadia 2014 France	Case series Retrospective	20	NR	<u>NRS</u> Baseline: 8.2*1 At 6 months: 5.1* At 6.1 years: 5.9 * (mean follow-up) Change at 6 months: - 38 % p< 0.001 pre – post comparison	None	Type of patients: 11 post-stroke, 4 trigeminal neuralgia, 2 spinal cord injury, 3 peripheral lesion. * estimated from Figure 1.	?	?	
		20		There was a significant association between CPA after rTMS and CPA 6 months after MCS (p = 0.02). A “good score” after rTMOS predicted pain relief of MCS with a Positive Predictive Value of 90 %, and a Negative Predictive Value of unsuccessful rTMS of 0.67.		The time interval between rTMS and surgical implantation of MCS was 6 months.			

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale;,
CPA = Combined Pain Assessment Score (-3; definite worsening, to + 3; definite improvement)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:5. Motor cortex stimulation in patients with chronic neuropathic pain. PICO 2
Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				MCS	Control group				
Hosomi 2008 Japan	Case series Retrospective	34		VAS Change at last follow-up: Men: - 43 % Females: - 36 %	None	Type of patients: 18 post-stroke, 1 pontine injury, 7 brachial plexus injury, 1 trigeminal neuralgia, 2 spinal cord injury, 4 spinal cord injury, 1 peripheral lesion.			
		11		There was a significant correlation (linear) between VAS reduction after rTMS and following MCS (p = 0.002).		The time interval between rTMS and surgical implantation of MCS was more than 2 weeks.			
Lefaucheur 20011 France	Case series Retrospective	59	NR	VAS Baseline: 8.0* At follow-up: 4.1* Change at follow-up: - 49 % p< 0.001 pre – post comparison	None	Type of patients: 20 post-stroke, 8 brachial plexus injury, 12 trigeminal neuralgia, 2 spinal cord injury, 12 spinal cord injury, 7 peripheral lesion. * estimated from Figure 2.			
		59		There was a significant correlation (Spearman) between VAS reduction after rTMS and VAS reduction after MCS (r= 0.31, p = 0.016). Response to rTMOS predicted pain relief of MCS with a Positive Predictive Value of 79 %, and a Negative Predictive Value of unsuccessful rTMS of 0.66 %.		The time interval between rTMS and surgical implantation of MCS was not reported.			

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale;,
CPA = Combined Pain Assessment Score (-3; definite worsening, to + 3; definite improvement)

* + No or minor problems
? Some problems
- Major problems

Appendix 4:5. Motor cortex stimulation in patients with chronic neuropathic pain. PICO 2
Outcome variable: Pain.

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				MCS	Control group				
Mandat 2012 Poland	Case series Retrospective	23		<u>VAS</u> Baseline: 8.3 At 3 months: 3.4 Change at 3 months: - 59 % p< 0.001 pre – post comparison	None	Type of patients: 8 post-stroke,4 trigeminal neuralgia, 3 spinal cord injury, 4 brachial plexus injury, 4 craniofascial surgery. 10/16 patients with rTMS prior to MCS had transient reduction of pain before MCS implantation.	-	?	
		16		6/16 patients did not have a good response to rTMS. They did neither respond to MCS. 10/16 patients had a good response to rTMS. They all responded to MCS.		The time interval between rTMS and surgical implantation of MCS was not reported.			

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale;,
CPA = Combined Pain Assessment Score (-3; definite worsening, to + 3; definite improvement)

* + No or minor problems ? Some problems - Major problems

Appendix 4:6. Diagnostic performance of rTMS to predict a response to motor cortex stimulation in patients with chronic neuropathic pain. PICO 2

Author, year, country	Study design	Number of patients n=			Predictive value		Comments
			Sensitivity	Specificity	Positive	Negative	
André-Obadia 2014 France	Case series Retrospective	20	60 % 95 % CI: 33 % to 83 %	75 % 95 % CI: 20 % to 99 %	90 % 95 % CI: 56 % to 99 %	33 % 95 % CI: 8 % to 70 %	Positive response: > 30 % Pain reduction on VAS
Hosomi 2008 Japan	Case series Retrospective	11	89 % 95 % CI: 52 % to 99 %	100 % 95 % CI: 16 % to 100 %	100 % 95 % CI: 64 % to 100 %	67 % 95 % CI: 10 % to 99 %	Positive response: ≥ 50 % Pain reduction on VAS
Lefaucheur 20011 France	Case series Retrospective	59	74 % 95 % CI: 57 % to 87 %	71 % 95 % CI: 49 % to 87 %	79 % 95 % CI: 62 % to 91 %	65 % 95 % CI: 45 % to 82 %	Positive response: > 30 % Pain reduction on VAS

Abbreviations: rTMS = repetitive Transcranial Magnetic Stimulation, VAS = Visual Analogous Scale.

Appendix 5. Ethical aspects on the use of neuromodulation in chronic neuropathic pain.

The effect of the intervention on health	
Q1*: Health: How does the intervention effect patients' health in terms of quality of life and life-length (including adverse effects)?	It probably has a positive effect. A reduction of pain will lead to an improved quality of life, and there are no serious adverse side effects.
Q2: Knowledge gaps: If there is lack of scientific evidence for the effect of the intervention, are there ethical and/or methodological problems with future research in order to strengthen this evidence.	No.
Q3: Degree of severity: What degree of severity has the condition the intervention is supposed to treat?	It is a severe condition causing major disability. It frequently leads to a severely reduced quality of life.
Q4: Third parties: How does the intervention affect the health of third parties?	In a positive way. The pain reduction for the patient will most probably positively affect family members and other third parties.
Summary: How is the benefit/risk – ration for the intervention (given the answers of Q1-Q4)?	Positive.
Q5: Equality and justice: Is there a risk that access to the intervention violates the Human Dignity principle or the Swedish Discrimination Act?	No.

Appendix 5. Ethical aspects on the use of neuromodulation in chronic neuropathic pain.

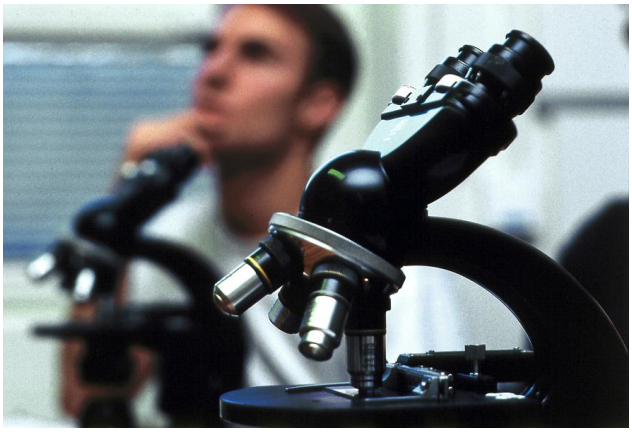
The compatibility of the intervention with ethical values	
Q6: Autonomy: Can the intervention affect patients' and significant others participation in decisions and there ability to make informed and relevant decisions about the intervention?	Yes.
Q7: Privacy: How does the intervention affect patient's and significant others' physical and personal privacy?	There are both positive and negative effects. One positive effect may be that a pain reduction will improve the patient's well-being and thereby secondarily positively affect the relationship towards others. Other positive effects may be that less money needs to be spent on pharmacotherapy and also that the potential risk for substance abuse will decrease. A negative effect may be more frequent hospital visits in order to receive treatment sessions due to its shorter duration of effect. Thus, the patient will be dependent on more frequent hospital visits and greater consumption of health care.
Q8: Cost effectiveness: Is the balance between the cost and effects of the intervention reasonable?	There is no cost effectiveness analysis available.
Summary: Is the use of the intervention compatible with ethical values (given the answers of Q5-Q8)?	Yes.
Structural factors that can affect the use and consequences of the intervention	
Q9: Resources and organisation: Are there resource- or organizational limitations that can affect who will get access to the intervention or that can lead to less access to other care if the intervention is used?	Yes, there are organisational resources and limitations. An introduction of both rTMS and MCS will require extra resources with regard to personnel and laboratory and operating rooms. This will most probably have consequences for other patient groups in terms of growing waiting lists and treatment delay.
Q10: Professional values: Can values within the affected care professions influence the use of the intervention and thereby lead to unequal access?	No.
Q11: Stake holder interests: Are there stake holder interests that can influence the use of the intervention and thereby lead to unequal access?	No.
Summary: Are there reason to believe that an equal access to the intervention (or other care interventions) can be affected (given the answers to Q9-Q11)?	Yes. Not all clinics that manage patients with chronic pain in Region Västra Götaland can offer this treatment.

Appendix 5. Ethical aspects on the use of neuromodulation in chronic neuropathic pain.

Long-term ethical consequences	
Q12: Long-term consequences: Can the use of the intervention result in more long-term consequences?	It is presently unknown whether there are any long-term side effects of this intervention.
Overall summary	
How can the ethical aspects regarding the intervention be summarised? Does this summary indicate that the intervention should be modified or that there should be special requirements associated with offering the intervention?	rTMS and MCS treatment comply well with most ethical demands. rTMS is a non-invasive treatment that is not likely to cause serious complications. The method makes it possible to treat patients that are resistant to other treatments. It will probably improve a patient's quality of life. However, not all clinics have access to these therapies. Therefore, not all patients that may benefit from this intervention may be offered the treatment. Another consequence might be that other categories of patients with different diagnoses may be negatively affected due to longer waiting list because of an increase number of patients.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

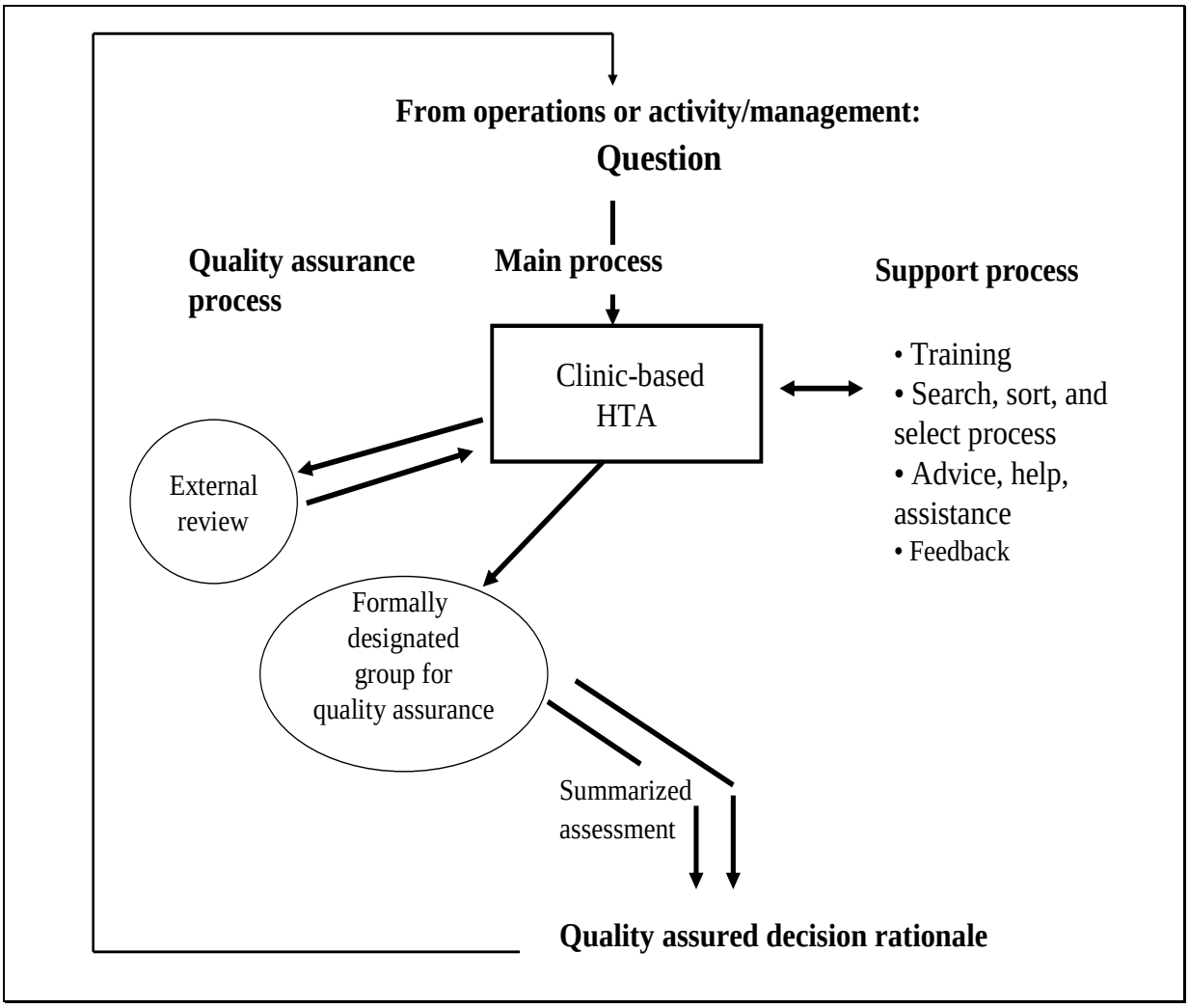
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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