Transcranial Magnetic Stimulation (TMS) for the Treatment of Pain

The NeuroStar TMS Therapy® system is a computerized electromechanical instrument that produces and delivers brief duration, rapidly alternating (pulsed) magnetic fields to induce electrical currents in localized regions of the cerebral cortex.

NeuroStar TMS Therapy is FDA-cleared for the treatment of Major Depressive Disorder (MDD) in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode (Demitrack & Thase, 2009).

In response to your request for information on the use of NeuroStar TMS Therapy in the treatment of pain, a summary of the literature has been provided for educational purposes only. NeuroStar TMS Therapy has not been cleared by the Food and Drug Administration for the treatment of pain. This information does not constitute a recommendation on the appropriateness of use of NeuroStar TMS Therapy for a particular patient. The benefit and risk of NeuroStar TMS Therapy for a specific patient should be evaluated prior to the beginning of any treatment.

The NeuroStar TMS Therapy System is contraindicated for use in patients who have conductive, ferromagnetic, or other magnetic-sensitive metals implanted in their head or are non-removable and within 30 cm of the treatment coil. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes. Failure to follow this restriction could result in serious injury or death. Examples of metallic objects in or near the head that are acceptable under certain conditions include standard amalgam dental fillings, single post dental implants, and dental bridge work.

The NeuroStar TMS Therapy System is contraindicated for use in patients who have active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators. Contraindicated use could result in serious injury or death.

For full safety and prescribing information for NeuroStar TMS Therapy, please refer to NeuroStarTMS.com.

Method of Review

A literature search was conducted on PubMed (www.pubmed.gov) for the terms “transcranial” and “magnetic” and “stimulation” and “pain” on January 12, 2012. Articles and book chapters, from 1991 until January 2012, related to TMS and pain are included in this summary. The types of papers reviewed include clinical trials of TMS for the treatment of pain, case studies of the use of TMS in pain conditions, and review articles. Additionally, two key textbooks on TMS were reviewed for data on TMS and pain (Epstein CM, 2007;Lefaucheur, 2008a).
The data summarized below focuses on the treatment of pain in patients with various pain conditions or symptoms, as reported in the clinical trial reports and reviews noted above. The Neotonus NeoPulse, an early version of the NeuroStar TMS Therapy System Therapy was studied in the following reports: Borckardt 2006 & 2009, Defrin 2007 and Short 2011, while O’Reardon 2007 used the Neuronetics model 2100 CRS TMS system, an early research version of the NeuroStar TMS Therapy System (Borckardt et al., 2009;Borckardt et al., 2006;Defrin et al., 2007;O’Reardon et al., 2007a;Short et al., 2011). All other studies reviewed in this summary used investigational TMS devices from other manufacturers.

**Summary of Data**

TMS has been studied as a treatment for a variety of different chronic pain syndromes including neuropathic pain, migraine headaches and fibromyalgia, and in an acute pain clinical setting (see Table 1). Various stimulation locations and treatment parameters have been investigated; however, most studies were conducted using TMS over the motor cortex region, usually applied contralateral to the location of the pain. In these studies of varied pain disorders, pain reduction was reported concurrent with the TMS treatment and was sustained for short periods of observation following cessation of TMS treatment. The duration of beneficial effect after a single TMS session was reported to be a few days to a week (Lefaucheur, 2008b). Multiple sessions over the motor cortex showed longer durability of effect with symptom improvement lasting 2-6 weeks after the last TMS treatment session (Defrin et al., 2007;Passard et al., 2007). A meta-analysis study that included 149 patients with neuropathic pain reported a significant pain reduction with TMS, especially in trigeminal neuropathic pain patients (28.8%) (Leung et al., 2009). However, a more recent meta-analysis study that included 267 patients with different types of chronic pain, reported that high-frequency TMS of the motor cortex induced a modest and transient pain reduction (15%) while low frequency TMS was ineffective (O’Connell et al., 2011).

Several studies of TMS treatment applied over the dorsolateral prefrontal cortex (DLPFC) have been reported. Short and colleagues reported that TMS targeted to the left DLPFC did not show advantage over sham in improving pain in 20 fibromyalgia patients (Short et al., 2011). Borckardt and colleagues reported a modest decrease of average daily pain (19%) in 4 neuropathic pain patients that lasts for 2 weeks after stimulating the left DLPFC at 10 pulses per second (pps) (referred to as Hz in some literature reports) (100% of Motor Threshold (MT), 4000 pulses per session (Borckardt et al., 2009). Avery and colleagues evaluated changes in pain symptoms in patients treated for depression (Avery et al., 2007). This study evaluated 68 patients in a sham-controlled trial, with stimulation over the left DLPFC, 110% of MT, with 10 Hz for 5 seconds of stimulation with intertrain interval of 25-30 seconds of stimulation off-time, for a total of 1600 pulses per session.
Each patient received 15 sessions of TMS. Improvement in pain symptoms was statistically significant in favor of active TMS, when compared between active and sham treatment conditions (p=0.04). Improvement of pain symptoms was observed at visit 5 and 10 but not at visits 15 and 16. Treatment occurred through visit 15, while visit 16 occurred one week after treatment was completed. Brighina and colleagues conducted a double-blind study in 11 migraine headache patients with TMS given at 20Hz for 10 total trains of 2 seconds on-time, intertrain interval of 20 seconds off-time at 90% MT over left DLPFC (Brighina et al., 2004). Each patient received 12 sessions, 3 per week for 4 weeks. The 6 patients given active TMS treatment showed symptom improvement of reduced frequency of migraines, less use of rescue medication, and lower headache index scores, one and two months after the study treatment started. All sham patients showed little or no change in clinical features after treatment.

O’Reardon and colleagues reported a case study of two patients (O’Reardon et al., 2007a). These patients participated in the NeuroStar TMS Therapy System pivotal trial (O’Reardon et al., 2007b). O’Reardon noted that during the clinical trial program, these patients seemed to have headache pain resolution coincident with TMS treatment and experienced return of symptoms upon cessation of treatments. These two patients were diagnosed with DSM-IV-defined major depressive disorder, and reported concurrent medical history with chronic headaches. Both patients were randomized into the double-blind study and received TMS treatment at 10Hz, 120% MT for 4 seconds of stimulation on-time, intertrain interval of 26 second stimulation off-time for 3000 pulses per session for 5 treatments per week (once daily). Both patients who received active treatment in the blinded study, did not show clinically significant improvement in depression symptoms after 4 weeks of treatment, and then entered a follow-up open label study of the same design. After completion of these studies, they both entered the maintenance of effect trial and then received compassionate use treatment in a study extension. In all studies, headache pain resolved for both patients during the active TMS treatment periods. In the compassion use trial in which the patients were treated two times per week, headache symptoms were also reported to resolve.

Borckardt and colleagues conducted a trial with an earlier research version of the NeuroStar TMS Therapy Systems in postoperative abdominal surgery patients, to evaluate reduction in analgesic use and the effect of TMS on acute pain (Borckardt et al., 2006). Twenty gastric bypass surgery patients were enrolled prior to surgery. Patients were randomized to active or sham treatment. Post-surgery, the patient’s MT level was calculated and patients were treated on the left DLPFC with 10Hz at 100% MT for 10 second stimulation time and intertrain interval of 20 second stimulation off-time for 20 minutes. Use of morphine loading, fentanyl, hydromorphone, ketorolac, or lidocaine use was evaluated for each patient 2 hours post-surgery. A significant difference was found between groups for midazolam use (p=0.04) but not for any other medication.
Cumulative milligrams of morphine used was significantly less in subjects receiving active TMS than in subjects receiving sham TMS 2 hours post-surgery, but was not reported as statistically significant.

For more information on TMS studies related to pain, there are a number of recent reviews of the data that can be consulted (Epstein CM, 2007; Fregni et al., 2007; Lefaucheur et al., 2008; Lefaucheur, 2008b). All recommend the need for additional data on the various treatment locations and whether or not a specific location is more effective than another for different causes of pain. The authors are inconclusive regarding the durability of acute TMS treatment for patients with chronic pain. Lefaucheur suggests that TMS treatment may serve as an intermediate treatment in some patients, prior to permanent implantation of a motor cortex stimulation patch (MCS) (Lefaucheur et al., 2008).

**Safety**

Borckardt and colleagues reported a higher incidence of headache in patients who received TMS vs. sham (50% vs 20%) (Borckardt et al., 2006). In all cases, the headaches were not severe and were managed using standard pain protocols.

No other studies reported adverse events.
### Table 1. Studies of TMS and Pain

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Author &amp; Year</th>
<th>No. of patients</th>
<th>Clinical trial design</th>
<th>TMS treatment</th>
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</thead>
</table>
| Neuropathic pain        | Lefaucheur et al. 2001 (Lefaucheur et al., 2001a) | 18              | Sham-controlled, cross-over | - Magstim Super Rapid stimulator  
- 0.5 or 10Hz  
- 80% of MT  
- 20 trains of 5sec (55sec intertrain interval)  
- 12 sessions | Intractable neuropathic pain (stroke, brain stem lesion, and brachial plexus lesion) | VAS (visual analogue scale) | There was a significant pain relief with 10Hz TMS. | The authors suggested that TMS is associated with transient pain relief. |
| Neuropathic pain        | Lefaucheur et al. 2001 (Lefaucheur et al., 2001b) | 14              | Sham-controlled, cross-over | - Magstim Super Rapid stimulator  
- 10Hz  
- 80% of MT  
- 20 trains of 5sec (55sec intertrain interval)  
- 12 sessions | Intractable neuropathic pain (stroke, trigeminal neuropathy) | VAS (in the evening after each session for 12 days) | There was a significant pain decrease in the first 8 days after treatment initiation.  
The difference between active TMS and sham from days 9 to 12 was not more significant. | The authors suggested that TMS may be a treatment option for transient pain relief in patients with chronic neuropathic pain. Limitations: small sample size that includes two types of pathologies. |
| Neuropathic pain        | Rollnik et al. 2002 (Rollnik et al., 2002) | 12              | Sham-controlled, cross-over | - Magstim Super Rapid stimulator  
- 20Hz  
- 80% of MT  
- 20 trains of 2sec  
- 800 pulses per session | Intractable chronic pain | VAS (before and after stimulation) | No significant differences between active and sham stimulation | |
| Migraine                | Brighina et al. 2004 (Brighina et al., 2004) | 11              | Sham (n=5), TMS (n=6) | - Cadwell high-frequency magnetic stimulator  
- 20Hz  
- 90% of MT  
- 10 trains of 2sec (30sec intertrain interval)  
- 12 sessions delivered at alternate days targeting the left DLPFC | Chronic migraine | Attack frequency, headache index, number of abortive medications (before, during and in the month after treatment) | There was a significant long-lasting (1 month after end of treatment) reduction in attack frequency, headache index and number of abortive pills as compared to sham. | The authors concluded that high-frequency TMS was able to ameliorate chronic migraine. |
| Neuropathic pain        | Lefaucheur et al. 2004 (Lefaucheur et al., 2004a) | 1               | Case-report | - Magstim Super Rapid stimulator  
- 10Hz  
- 80% of MT  
- 20 trains of 5sec (55sec intertrain interval)  
- 16 months of monthly sessions | Intractable neuropathic pain (stroke, SCI, brachial plexus lesion, and trigeminal neuropathy) | VAS | The patient experienced pain relief for a week and then it returned progressively to its initial level.  
Pain intensity was reduced by 40% after real TMS and by 15% after sham session | |
| Neuropathic pain        | Lefaucheur et al. 2004 (Lefaucheur et al., 2004b) | 60              | Sham-controlled, cross-over | - Magstim Super Rapid stimulator  
- 10Hz  
- 80% of MT  
- One session of 20 trains of 5sec (55sec intertrain interval) | Intractable unilateral neuropathic pain (trigeminal neuralgia, post-stroke pain syndrome) | VAS (before and after session) | There was a significant but transient pain reduction vs. sham.  
Pain level was reduced in 65% of the patients. The best results were obtained in patients with trigeminal neuropathy. | The authors suggested that a single session of TMS could reduce pain level in patients with chronic intractable neuropathic pain. TMS efficacy can be influenced by pain origin, pain site, and sensory loss within the painful area. |
| Neuropathic pain        | Khedr et al. 2005 (Khedr et al., 2005) | 48              | Sham-controlled | - 20Hz  
- 80% of MT  
- 10min for 5 consecutive days | Therapy resistant chronic unilateral pain (trigeminal neuralgia, post-stroke pain syndrome) | VAS and Leeds assessment of neuropathic symptoms and signs (LANSS)(Before and after the 1st, 4th, and 5th session and 2 weeks after the last session) | There was greater improvement in VAS and LANSS scores vs. sham | The authors suggested that TMS can reduce pain ratings in patients with neuropathic pain during the treatment and at least 2 weeks after the end of treatment. |
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<td>Neuropathic pain</td>
<td>Andre’-Obadia et al. 2006 (Andre-Obadia et al., 2006)</td>
<td>14</td>
<td></td>
<td>- Magstim Super Rapid stimulator</td>
<td>Chronic neuropathic pain resistant to medication (stroke, SCI or peripheral lesion)</td>
<td>VAS (Before and immediately after TMS every day for 2 weeks)</td>
<td>VAS was significantly decreased immediately after the TMS session, with any of the types of stimulation applied (sham, 1Hz, 20Hz). 20Hz was superior over 1Hz to decrease pain during the week following the stimulation session.</td>
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<td>Postoperative pain</td>
<td>Borckardt et al. 2006 (Borckardt et al., 2006)</td>
<td>20</td>
<td></td>
<td>- Neotonus Neopulse device</td>
<td>Gastric bypass surgery</td>
<td>VAS and analgesia pump use</td>
<td>TMS was associated with a 40% reduction in total morphine use compared with sham during the 44h after surgery. The authors suggested that a single 20min postoperative TMS session may reduce morphine usage. The effect seems more pronounced during the first 24h. Limitations: blinding and small sample size may limit generalizability for other surgical patients.</td>
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<td>Migraine</td>
<td>Clarke et al. 2006 (Clarke et al., 2006)</td>
<td>42</td>
<td></td>
<td>- Cadwell stimulator</td>
<td>Migraine (ICHD-II classification)</td>
<td>Likert Pain Scale (before and after stimulation at 5min intervals for 20min)</td>
<td>Overall mean decrease in pain intensity of 75%. 69% showed improvement with 1 trial, 87% with 2 trials and 82% with 3 trials. All patients with aura had immediate relief. Improvement was shown after an average of 15min. 32%, 29% and 40% were headache free after 24 h after 1, 2, and 3 trials, respectively. 24%, 35% and 60% did not take rescue medication for 24 h after 1, 2, and 3 trials, respectively. The authors suggested that TMS may “normalize” the autonomic nervous system and subsequently modify the vasodilation of meningeal blood vessels in migraine</td>
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<td>Neuropathic pain</td>
<td>Hirayama et al. 2006 (Hirayama et al., 2006)</td>
<td>20</td>
<td></td>
<td>- MC B-70 (Medtronic)</td>
<td>Intractable deafferentiation pain (post-stroke, SCI, trigeminal neuropathic pain, and brachial plexus injury)</td>
<td>VAS, MPQ (short form) (before and after 0,30,60,90 and 180 min) A responder to TMS was defined by an improvement in VAS scores of more than 30%.</td>
<td>TMS over the motor cortex (and not other regions) was associated with significant pain relief in 50% of the patients that lasted for 3h after stimulation.</td>
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<td>Chronic back pain</td>
<td>Johnson et al. 2006 (Johnson et al., 2006)</td>
<td>17</td>
<td>Sham-controlled</td>
<td>- Magstim Super Rapid stimulator</td>
<td>BPI</td>
<td></td>
<td>13/17 of the patients reported a decrease in pain intensity while sham treatment did not induce a significant change in pain rating.</td>
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<td>Neuropathic pain</td>
<td>Lefaucheur et al. 2006 (Lefaucheur et al., 2006b)</td>
<td>36</td>
<td>- Sham-controlled, cross-over</td>
<td>- Magstim Super Rapid stimulator - 10Hz - 90% of MT - 20 trains of 10sec (50sec intertrain interval)</td>
<td>Unilateral chronic pain located at the face or the hand</td>
<td>VAS</td>
<td>There was a significant reduction in pain scores as compared to baseline. In patients with facial pain, the averaged pain scores improved by 27% after TMS was targeted to the corresponding hand area in the cortex. 8/18 patients with facial pain experienced significant pain relief after TMS was targeted to the corresponding hand area in the cortex. 11/18 patients with hand pain experienced significant pain relief after TMS was targeted to the corresponding face area in the cortex.</td>
<td>The authors suggested that TMS significantly relieved pain compared to baseline.</td>
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<td>Neuropathic pain</td>
<td>Lefaucheur et al. 2006 (Lefaucheur et al., 2006a)</td>
<td>22 patients and 22 healthy controls</td>
<td>- Sham-controlled, double-blind</td>
<td>- Magstim Super Rapid stimulator - 1 or 10Hz - 90% of MT - 20 trains of 6sec (54sec intertrain interval)</td>
<td>Unilateral hand pain</td>
<td>10Hz TMS was associated with intracortical inhibition increase in the motor cortex corresponding to the painful hand in correlation with pain relief.</td>
<td>10Hz TMS was associated with intracortical inhibition increase in the motor cortex corresponding to the painful hand in correlation with pain relief.</td>
<td>The authors suggested that the analgesic effect produced by TMS could results from the restoration of defective intracortical inhibitory processes.</td>
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<td>Fibromyalgia</td>
<td>Sampson et al. 2006 (Sampson et al., 2006)</td>
<td>4</td>
<td>- Sham-controlled, double-blind</td>
<td>- Magstim Super Rapid stimulator - 1Hz - 110% of MT - 2 trains of 800sec (60sec intertrain interval) - 1600 pulses per session targeting the right dorsolateral prefrontal cortex - 4 weeks</td>
<td>Likert Pain Scale</td>
<td>All patients noted an improvement in pain while 2 patients reported complete resolution of pain</td>
<td>Limitations: small sample size and potential confound from comorbid borderline personality disorder</td>
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<td>Pain in patients with MDD</td>
<td>Avery et al. 2007 (Avery et al., 2007)</td>
<td>68</td>
<td>- Sham-controlled study</td>
<td>- Dantec Magpro magnetic stimulator (Medtronic) - 10Hz - 110% of MT - 1600 pulses per session - 5sec (25-30sec intertrain interval) - 15 TMS sessions targeted to the left dorsolateral prefrontal cortex in 4 weeks</td>
<td>MDD (based on DSM-IV) A core of 17 or greater on the Hamilton Depression Rating scale-17</td>
<td>Systematic assessment for treatment emergent effects (SAFTEE) for pains in the muscles, bones, and joints</td>
<td>There was a significant reduction in SAFTEE pain items as compared to sham at visits 5 and 10 but not at visits 15 and 16.</td>
<td>The authors suggested that TMS was associated with reduction in self-reported pain. Limitations: small sample size, imprecise assessment of pain, varied types of pain and chronicity.</td>
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| Spinal cord injury         | Defrin et al. 2007 (Defrin et al., 2007) | 12             | Double-blind, randomized, controlled study | -Neotonus magnetic stimulator  
-5Hz  
-115% of MT  
-500 trains of 10sec (30sec intertrain interval)  
-10 daily sessions over 2 weeks | Paraplegic patients due to thoracic SCI | VAS; MPQ  
Pain threshold | Both real and sham TMS were associated with reduction in VAS and MPQ scores after each treatment. Real TMS increased heat-pain threshold. | The authors concluded that there were not significant differences between real and sham TMS |
| Migraine                   | O’Reardon et al. 2007 (O’Reardon et al., 2007a) | 2              | Case-report                     | -10Hz  
-120% of MT  
-3000 pulses per session over the left dorsolateral prefrontal cortex  
-5 daily sessions over 4-6 weeks followed by maintenance therapy over 2-years | MDD | Reduction in migraine frequency | | |
| Fibromyalgia               | Passard et al. 2007 (Passard et al., 2007) | 30             | Randomized, double-blind sham-controlled parallel group study (sham (n=15); TMS (n=15)) | - Magstim Super Rapid stimulator  
-10Hz  
-80% of MT  
-25 trains of 8sec (52sec intertrain interval)  
-2000 pulses per session  
-10 daily sessions | ACR criteria to fibromyalgia and suffered persistent pain for more than 6 months. | Primary: pain intensity before, daily during the stimulation period and 15,30, and 60 days after the first stimulation  
Secondary: MPQ and pressure pain threshold | There was a significant pain reduction from day 5 to day 14 with active TMS. On day 15 MPQ score were significantly lower than sham. TMS did not affect the number of tender points. There was a significant increase in pressure pain threshold following TMS. | The authors suggested that high-frequency TMS can reduce neuropathic pain. Patients with a noncerebral lesion are more suitable candidates for TMS. |
| Neuropathic pain           | Saitoh et al., 2007 (Saitoh et al., 2007) | 13             | Sham-controlled, cross-over     | - MC B-70, Medtronic  
-1, 5 or 10Hz  
-90% of MT  
-10 trains of 10sec (50sec intertrain interval)  
-Single session of 500 pulses | Intractable deafferentiation pain (stroke, SCI, brachial plexus injury, peripheral nerve injury, cuada equine lesion, or a phantom limb) | VAS and MPQ (before and after 0,15,30,60,90 and 180min) | 5 and 10Hz TMS were associated with a significant pain reduction as compared to sham that continued for 180min. The effect was greater in patients with a noncerebral lesion than those with cerebral lesion. | The authors suggested that high-frequency TMS can reduce neuropathic pain. Patients with a noncerebral lesion are more suitable candidates for TMS. |
| Central post-stroke pain   | Goto et al. 2008 (Goto et al., 2008) | 17             | Pilot                           | - MagPro magnetic stimulator  
-5Hz  
-90% of MT  
-Single session of 10 trains of 10sec (50sec intertrain interval)  
-over the motor cortex | VAS Effectiveness was defined as a decrease of more than 30% in the VAS score | VAS | There was a reduction of more than 30% in the VAS score in 8/17 of patients. | The authors suggested that intact corticospinal tract neurons are required for effective pain treatment. |
| Neuropathic pain           | Andre’-Obadia et al. 2008 (Andre’-Obadia et al., 2008) | 28             | Double-blind, randomized, cross-over study | - Magstim Super Rapid stimulator  
-20Hz  
-90% of MT  
-Single session of 1600 pulses  
-Coil orientation: posteroanterior vs. lateromedial motor cortex | VNS (visual numerical scale) (after each TMS session and the end of each day for 2 weeks) | Pain scores differences between sham and real TMS were more pronounced on days 3 and 4. The mean analgesic effect was modest (14% of VNS decrease). | | |
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| Neuropathic pain        | Lefaucheur et al. 2008 (Lefaucheur et al., 2008) | 46              | Sham-controlled, cross-over  | - Magstim Super Rapid stimulator  
- 1 or 10Hz  
- 90% of MT  
- 20 trains of 6sec (54sec intertrain interval)  
- Single session of 1200 pulses | Medication-resistant to at least 2 drug classes for more than 1 year (trigeminal neuropathy, brachial plexus lesion, stroke, and SCI) | VAS (before and after session); changes in sensory threshold | There was a significant pain reduction as well as lowered thermal sensory thresholds but not mechanical sensory thresholds. |                                                                                                                                            |
| Spinal cord injury      | Kang et al. 2009 (Kang et al., 2009) | 13              | Blinded, randomized, cross-over | - 10Hz  
- 80% of MT  
- 20 trains of 5sec (55sec intertrain interval)  
- 1000 pulses per session  
- 5 daily sessions targeting the hand motor cortex | SCI (complete or incomplete) with chronic neuropathic pain for 15 months or more and was resistant to medication | Numeric Rating Scale (NRS) at days 3 and 5 and weeks 1,3,5, and 7 of follow-up  
BPI | No differences between pain intensities between sham and TMS. | No efficacy was demonstrated                                                                                   |
| Neuropathic pain        | Borckardt et al. 2009 (Borckardt et al., 2009) | 4               | Single-blinded, sham-controlled, crossover | - Neotonus Neopulse  
- 10 Hz  
- 100% of MT  
- 10sec (20sec intertrain interval)  
- 4000 pulses per session  
- 3 sessions of TMS and 3 session of sham (separated by 3 weeks) targeting the left prefrontal cortex | Neuropathy Pain Scale (NPS); BPI | TMS was associated with a decrease of average daily pain (19%) that lasts for 2 weeks | The limitations of the study: Small sample size, different neuropathic pain types |                                                                                                                                            |
| Neuropathic pain        | Leung et al. 2009 (Leung et al., 2009) | 149             | Meta-analysis               | Neuronal pain attributed to neuroanatomical origin (Peripheral nerve (PN); Nerve root (NR); Spinal cord (SC); Trigeminal nerve or ganglion (TGN); Post-stroke supraspinal related pain (PSP); Primary motor cortex as the treatment site VAS as primary outcome | | Significance pain reduction with TMS as compared to sham. The TGN group had the greatest effect (28.8%), followed by PSP (16.7%), SC (14.7%), NR (10%) and PN (1.5%). | The authors suggested that TMS can provide significant pain reduction in patients with neuropathic pain. More studies regarding the dose and number of sessions are warranted. |                                                                                                                                            |
| Fibromyalgia            | Carretero et al. 2009 (Carretero et al., 2009) | 28              | Randomized, single-blinded  
Sham (n=12); TMS (n=14) | - DANTEC, MagLite model  
- 1 Hz  
- 110% of MT  
- 20 trains for 60sec (45sec intertrain interval)  
- 1200 pulses per session  
- 20 sessions targeting the right dorsolateral prefrontal cortex | | Linkert Pain Scale | No reduction in pain was observed with TMS. |                                                                                                                                            |
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<td>Migraine with aura</td>
<td>Almaraz et al. 2010 (Almaraz et al., 2010)</td>
<td>164</td>
<td>Double-blind, sham-controlled</td>
<td>-2 pulses 30sec apart</td>
<td>Pain-free rate (PFR) at 2h</td>
<td>There was a significant higher PFR in active TMS than sham in patients taking prophylactic medications. However no significant differences were detected between TMS and sham in patients that do not take medications. There was no difference in PFR between TMS-treated patients on prophylactic medications vs. TMS-patients without prophylactic medications. The authors suggest that there is no synergistic effect between TMS and prophylactic medication use and that prophylactic medications do not appear to influence the response to TMS. Limitations: Small sample size</td>
<td>The authors suggest that TMS may be efficacious as an add-on therapy to refractory CRPS type 1 patients</td>
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<td>Complex regional pain syndrome (CRPS)</td>
<td>Picarelli et al. 2010 (Picarelli et al., 2010)</td>
<td>23</td>
<td>Double-blind, placebo-controlled, 2-arm, randomized</td>
<td>-10 Hz -100% of MT -25 trains of 10sec (60sec intertrain interval) -2500 pulses per session -10 daily sessions targeting the precentral gyrus</td>
<td>VAS (daily pain was recorded for 2 weeks and after 1 week and 3 months of follow-up) McGill Pain Questionnaire (MPQ)</td>
<td>There was a significant VAS reduction from baseline as compared to sham (P&lt;0.05). Max pain relief was achieved after 10 sessions. The differences between TMS and sham were not maintained after 1 week or 3 months. The authors suggested that TMS may be efficacious as an add-on therapy to refractory CRPS type 1 patients</td>
<td>The authors suggested that TMS may be efficacious as an add-on therapy to refractory CRPS type 1 patients</td>
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<td>Migraine with aura</td>
<td>Lipton et al. 2010 (Lipton et al., 2010)</td>
<td>201</td>
<td>Randomized, double-blind, parallel-group, sham-controlled, 18 centers in the US (sham n=99; TMS n=102)</td>
<td>-Cerena TMS -Rise time of 180µs and a total pulse length of less than 1ms. -Single session of 2 pulses, 30sec apart</td>
<td>Migraine with aura Visual aura preceding at least 30% of migraines followed by moderate to severe headache</td>
<td>Primary: pain-free at 2h after treatment Secondary: sustained pain-free at 24h and 48h, headache response at 2h, use of rescue drugs and consistency of pain relief response.</td>
<td>Pain-free response rates after 2h were significantly higher in TMS (39%) than with sham (22%). Pain-free response rate at 24h and 48h after treatment significantly favored TMS over sham. The analgesic effect of TMS vs. sham was more notable when the baseline pain was moderate or severe and not mild. The authors concluded that there were significant differences TMS and sham in the primary and some secondary outcomes. However, some secondary outcomes did not differ between TMS and sham. The limitations of the study are that they didn’t explore different doses of TMS as well as optimum timing of treatment.</td>
<td>The authors concluded that there were significant differences TMS and sham in the primary and some secondary outcomes. However, some secondary outcomes did not differ between TMS and sham. The limitations of the study are that they didn’t explore different doses of TMS as well as optimum timing of treatment.</td>
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<td>Spinal cord injury spasticity</td>
<td>Kumru et al. 2010 (Kumru et al., 2010)</td>
<td>15</td>
<td>Sham (n=7); TMS (n=14), 6 crossed-over from the sham to TMS</td>
<td>-Magstim Super Rapid stimulator -20 Hz -90% of MT -20 trains of 40 pulses (28sec intertrain interval) -1600 pulses per session -5 daily sessions targeting the leg motor area</td>
<td>Incomplete SCI</td>
<td>There was a significant MAS reduction from baseline as compared to sham at the end of the first and last sessions (P&lt;0.006). The effect was maintained after one week of follow-up (P=0.049).</td>
<td>There was also significant MPSFS and SCAT reduction from baseline as compared to sham. The authors suggested that high-frequency TMS over the leg primary motor cortex can modulate spasticity in patients with incomplete SCI.</td>
<td>The authors suggested that high-frequency TMS over the leg primary motor cortex can modulate spasticity in patients with incomplete SCI.</td>
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<tr>
<td>Diagnosis</td>
<td>Author &amp; Year</td>
<td>No. of patients</td>
<td>Clinical trial design</td>
<td>TMS treatment</td>
<td>Inclusion criteria</td>
<td>Outcome measures</td>
<td>Results</td>
<td>Conclusions</td>
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<td>Chronic pancreatitis</td>
<td>Frengi et al. 2010 (Frengi et al., 2010)</td>
<td>17</td>
<td>Randomized, Sham-controlled (sham (n=82); TMS (n=82))</td>
<td>-Magstim Super Rapid Stimulator -1 Hz -1600 pulses per session -10 sessions over 2 weeks targeting of the right secondary somatosensory cortex</td>
<td>Daily abdominal pain for at least 3 months Ave VAS &gt; 4</td>
<td>VAS</td>
<td>There was a significant reduction in pain that maintained at least 3 weeks (P=0.015). At end of the first week, there was a mean decrease in pain levels of 27.2% in the TMS group versus an increase in pain levels of 1.1% in the sham group</td>
<td>The authors suggested that modulation of the right secondary somatosensory cortex with TMS is associated with a significant analgesic effect</td>
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<td>Neuropathic pain</td>
<td>Lefaucheur et al. 2011 (Lefaucheur et al., 2011)</td>
<td>59 (Stroke n=20; SCI n=12; Peripheral facial pain n=12; Limb nerve lesion n=15)</td>
<td>Sham-controlled, cross-over (Active and sham sessions were separated by more than 3 weeks)</td>
<td>-Super-Rapid Magstim -10 Hz -90% of MT -20 trains of 10sec (30sec intertrain interval) -Single session of 2000 pulses per session</td>
<td>Patients elected for epidural motor cortex stimulation. Pain was refractory to at least 3 different types of analgesics.</td>
<td>VAS (daily pain was recorded for 1 week after the session). A good responder to TMS was defined by an active-sham percentage of pain relief equal or greater than 30%</td>
<td>Pain scores (VAS) were reduced by active TMS but not by sham TMS (P&lt;0.0001). The analgesic effect (% change in pain score) of active TMS was greater than that of sham TMS (P &lt; .0001).</td>
<td>The authors suggested that neuropathic pain can be relieved by motor cortex TMS</td>
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<td>Fibromyalgia</td>
<td>Short et al. 2011 (Short et al., 2011)</td>
<td>20</td>
<td>Randomized (Sham (n=10); real TMS (n=10))</td>
<td>-NeoPulse Neotonus Model 3600 -10 Hz -120% of MT -4000 pulses per session Trains of 5sec (10sec intertrain interval) -10 sessions over 2 weeks targeting the left dorsolateral prefrontal cortex.</td>
<td>Fibromyalgia Primary: VAS (after 1 and 2 weeks of treatment and after 1 and 2 weeks of follow-up) Secondary: Brief Pain Inventory (BPI)</td>
<td>Mean pain ratings decreased significantly from baseline in the real TMS-treated group after 1 week of treatment but not in the sham (max reduction of 29% after 2 weeks). After 2 weeks of follow-up, the mean pain ratings were still significantly lower than baseline however, there were no statistically significant differences in mean pain scores between sham and real TMS.</td>
<td>The authors concluded that TMS did not show advantage over sham in improving pain in Fibromyalgia. Larger studies are needed to show the efficacy of TMS in patients with Fibromyalgia.</td>
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<td>Chronic pain</td>
<td>O’Connell et al. 2011 (O’Connell et al., 2011)</td>
<td>N=368 (pooled data from low or unclear risk of bias) N=267 (after correction for multiple comparisons)</td>
<td>Meta-analysis (years 2000-2010)</td>
<td>VAS</td>
<td>Single-dose high frequency TMS applied on the motor cortex has beneficial short-term effect. Multiple-dose studies have shown conflicting results with substantial heterogeneity.</td>
<td>The authors suggested that low frequency stimulation is ineffective. High-frequency stimulation of the motor cortex was suggested to have a short-term effect on pain. However 15% reduction in pain has borderline clinical importance. Studies’ limitations include: sub-optimal sham controls, insufficient data about the stimulation of other cortical area, different types of chronic pain etc.</td>
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<td>Fibromyalgia</td>
<td>Mhalla et al. 2011 (Mhalla et al., 2011)</td>
<td>40 females</td>
<td>Randomized, double-blind, sham-controlled parallel group study (sham (n=20); TMS (n=20))</td>
<td>-MagPRO X100 -10 Hz -80% of MT -15 trains of 10sec (50sec intertrain interval) -1500 pulses per session Daily stimulations for 5 days, followed by single stimulation sessions at week 1,2,3,5,7,9,13,17 and 21. Total of 14 sessions over 21 weeks and one follow-up at week 25.</td>
<td>Persistent pain for more than 6 months At least BPI=4</td>
<td>Primary: BPI Secondary: sensory and affective pain dimensions and the impact of pain and fibromyalgia on quality of life</td>
<td>Average pain intensity was significantly reduced after active TMS as compared to sham (P=0.007). The effect was significant from day 5 and lasted until week 25.</td>
<td>The authors suggest that TMS of the motor cortex can induce analgesic effect that can be maintained for up to 6 months in Fibromyalgia patients.</td>
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<td>Poststroke central pain</td>
<td>Ohn et al. 2012 (Ohn et al., 2012)</td>
<td>22</td>
<td>- Magstim Rapid2 -10 Hz -90% of MT -1000 pulses per session -50 trains of 5sec (55sec intertrain interval) -5 consecutive daily sessions targeting the motor hotspot of the affected hemisphere</td>
<td>Poststroke central pain over 6 months (pain level&gt;5) that was resistant to 2 or more medications</td>
<td>VAS, HDRS (before and after 5 and 14 days)</td>
<td>14/22 patients responded vs. 8/22 that did not respond. TMS was not associated with significant differences in VAS scores before and after treatment. There was a very modest and significant pain relief only in the responders group which lasted for 2 weeks.</td>
<td>The authors suggested that high-frequency TMS can produce a partial antalgic effect on poststroke central pain. Integrity of the thalamocortical tract showed significant correlation with pain relief after TMS. Distribution of stroke lesion was not associated with VAS change after TMS. Limitations: no-sham, small sample size</td>
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References


O'Reardon, J. P., et al., 2007a. Unexpected reduction in migraine and psychogenic headaches following rTMS treatment for major depression: a report of two cases. CNS Spectr. 12, 921-5.


Picarelli, H., et al., 2010. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. J Pain. 11, 1203-10.


