Transcranial Magnetic Stimulation and Cranial Electrical Stimulation

Aetna considers repetitive transcranial magnetic stimulation (rTMS) in a healthcare provider's office medically necessary when the following criteria are met:

- Administered by an FDA cleared device and utilized in accordance with the FDA labeled indications; and
- The member is age 18 years or older; and
- The member has a confirmed diagnosis of severe major depressive disorder (single or recurrent episode), documented by standardized rating scales that reliably measure depressive symptoms (e.g., Beck Depression Scale [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], etc.); and
- There is documentation via legible medical records of failure of a trial of a psychotherapy known to be effective in the treatment of major depressive disorder of an adequate frequency and duration, without significant improvement in depressive symptoms, as documented by standardized rating scales that reliably measure depressive symptoms (e.g., Beck...
Depression Scale [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], etc.; and

- The member is currently receiving or is a candidate for electroconvulsive therapy (ECT) and rTMS is considered a less invasive equally effective treatment option (e.g., in cases with psychosis, acute suicidal risk, catatonia or life-threatening inanition rTMS should not be utilized); and
- The member has no contraindications to rTMS (refer to contraindications below); and
- The member meets one of the following criteria:
  - There is documentation via legible medical records of failure of 4 trials of antidepressant agents, including 2 different agent classes, during the current depressive episode; or
  - The member is unable to tolerate a therapeutic dose of medications as evidenced by documentation via legible medical records of 4 trials of psychopharmacologic agents with distinct side effects; and

- Treatment consists of a maximum of 30 sessions (5 days a week for 6 weeks) plus 6 tapering sessions. Notes: Treatments beyond 36 sessions (e.g., 30 treatment sessions followed by 6 tapering sessions) may be reviewed for medical necessity. There is a lack of evidence that persons who fail to respond or become refractory to one brand of rTMS device will respond to another brand of rTMS device.

Aetna considers rTMS contraindicated and experimental and investigational in persons with any of the following contraindications to rTMS because the safety and effectiveness in person with these contraindications has not been established:

- Persons with high alcohol or illicit drug consumption; or
- The member is suicidal; or
- The member has a metal implant in or around the head (e.g., aneurysm coil or clip, metal plate, ocular implant, stent); or
- The member has neurological conditions (e.g., cerebrovascular disease, dementia, history of repetitive or severe head trauma, increased intracranial pressure or primary or secondary tumors in the central nervous system); or
- There is presence of implanted devices, (eg, cardiac pacemaker or defibrillator, cochlear implant, deep brain stimulator, implantable infusion pump, spinal cord stimulator, vagus nerve stimulator, etc.); or
- The member has a seizure disorder/epilepsy; or
- If the member has severe cardiovascular disease, he has been evaluated and cleared for rTMS treatment by a cardiologist.

Aetna considers rTMS maintenance therapy for depression to be experimental and investigational because the effectiveness and safety of rTMS maintenance therapy has not been established.

Aetna considers transcranial magnetic stimulation experimental and investigational for the following indications because its value and effectiveness has not been established (not an all-inclusive list):

- Alzheimer's disease
- Amyotrophic lateral sclerosis
- Anxiety disorders
- Auditory verbal hallucinations
- Autism
- Blepharospasm
- Bulimia nervosa
- Chronic pain including neuropathic pain (e.g., orofacial pain, and central post-stroke pain)
- Communication and swallowing disorders (e.g., aphasia (including post-stroke aphasia), dysarthria, dysphagia (including post-stroke dysphagia), and linguistic deficits)
- Complex regional pain syndrome
- Differential diagnosis of Alzheimer disease from frontotemporal dementia
- Epilepsy (including status epilepticus)
- Congenital hemiparesis
- Dystonia
- Fibromyalgia
- Levodopa-induced dyskinesia
- Migraine
- Mood disorders
- Neuropathic pain associated with spinal cord injury
- Obsessive-compulsive disorder

http://www.aetna.com/cpb/medical/data/400_499/0469.html 03/28/2019
- Panic disorder
- Parkinson disease
- Phantom pain associated with spinal cord injury
- Post-traumatic stress disorder
- Restless legs syndrome
- Schizophrenia
- Smell and taste dysfunction (e.g., phantosmia and phantageusia)
- Spasticity
- Stroke treatment (e.g., motor impairment, and post-stroke hemiplegia)
- Substance addiction
- Tourette syndrome
- Tinnitus
- Traumatic brain injury
- Visual hallucinations after stroke.

Aetna considers navigated transcranial magnetic stimulation experimental and investigational for motor function mapping and/or treatment planning of neurological diseases/disorders (e.g., amyotrophic lateral sclerosis, epilepsy, and resection of brain tumors) because its value and effectiveness has not been established.

Aetna considers cranial electrical stimulation (also known as cerebral electrotherapy, craniofacial electrostimulation, electric cerebral stimulation, electrosleep, electrotherapeutic sleep, transcerebral electrotherapy, transcranial electrotherapy, as well as the Fisher Wallace stimulator (formerly known as the Liss Body Stimulator) that is used to treat alcoholism) experimental and investigational because its value and effectiveness has not been established. It is not covered for any indication, including the following (not an all-inclusive list):

- Alcoholism
- Alzheimer’s disease
- Autism
- Chemical dependency
- Chronic pain
- Dementia
- Depression
- Disorders of consciousness
- Headaches
- Fibromyalgia
- Mood and sleep disturbances
- Neuropathic pain
- Parkinson disease
- Phantom pain associated with spinal cord injury
- Restless legs syndrome
- Stroke treatment (e.g., motor impairment, post-stroke aphasia, and post-stroke hemiplegia)
- Traumatic brain injury
- Visual rehabilitation.

Background

Transcranial magnetic stimulation (TMS) is a non-invasive method of induction of a focal current in the brain and transient modulation of the function of the targeted cerebral cortex. This procedure entails placement of an electromagnetic coil on the scalp; high-intensity electrical current is rapidly turned on and off in the coil through the discharge of capacitors. Depending on stimulation parameters (frequency, intensity, pulse duration, stimulation site), repetitive TMS (rTMS) to specific cortical regions can either increase or decrease the excitability of the affected brain structures.

Transcranial magnetic stimulation has been investigated in the treatment of various psychiatric disorders, especially depression. This procedure is usually carried out in an outpatient setting. In contrast to electroconvulsive therapy, TMS does not require anesthesia or analgesia. Furthermore, it does not affect memory and usually does not cause seizures. However, the available peer-reviewed medical literature has not established the effectiveness of rTMS in the treatment of psychiatric disorders other than major depression. In addition, more research is needed to ascertain the roles of various stimulation parameters of rTMS for its optimal outcome as well as its long-term effectiveness in the treatment of psychiatric disorders.

Depression

Martin et al (2003) conducted a systematic review of randomized controlled trials that compared rTMS with sham in patients with depression. The authors concluded that current trials are of low quality and provide insufficient evidence to support the use of rTMS in the treatment of depression. This is in accordance with the observations of Fitzgerald and colleagues (2002) who noted that TMS has a
considerable role in neuropsychiatric research. It appears to have considerable potential as a therapeutic tool in depression, and perhaps a role in several other disorders, although widespread application requires larger trials and establishment of sustained response, as well as Gershon et al (2003) who stated that TMS shows promise as a novel anti-depressant treatment. Systematic and large-scale studies are needed to identify patient populations most likely to benefit and treatment parameters most likely to produce success.

A health technology assessment prepared for the Ontario Ministry of Health and Long-Term Care (2004) concluded: "Due to several serious methodological limitations in the studies (Level 2 to 4 evidence) that examined the effectiveness of rTMS in patients with MDD [major depressive disorder], to date, it is not possible to conclude that rTMS is effective or not effective for the treatment of MDD (treatment resistant or not treatment resistant MDD)."

Nemeroff (2007) stated that the role of non-pharmacological therapies such as electro-convulsive therapy (ECT), vagus nerve stimulation (VNS), deep brain stimulation (DBS), and TMS in the treatment of patients with severe depression remain active avenues of investigation.

A randomized clinical trial (RCT) conducted for the National Coordinating Centre for Health Technology Assessment found that ECT is a more effective and potentially cost-effective antidepressant treatment than 3 weeks of rTMS (McLoughlin et al, 2007). A total of 46 patients with major depression were randomized to receive a 15-day course of rTMS (n = 24) or a course of ECT (n = 22). One patient was lost to follow-up at end of treatment and another 8 at 6 months. The end-of-treatment Hamilton Rating Scale for Depression (HRSD) scores were lower for ECT (95% confidence interval (CI): 3.40 to 14.05, p = 0.002), with 13 (59%) achieving remission compared with four (17%) in the rTMS group (p = 0.005). However, HRSD scores did not differ between groups at 6 months. Beck Depression Inventory-II (BDI-II), visual analogue mood scales (VAMS), and Brief Psychiatric Rating Scale (BPRS) scores were lower for ECT at end of treatment and remained lower after 6 months. Improvement in subjective reports of side-effects following ECT correlated with anti-depressant response. There was no difference between the 2 groups before or after treatment on global measures of cognition. The NCCHTA study also evaluated the comparative costs of ECT and rTMS. The investigators reported that, although individual treatment session costs were lower for rTMS than ECT, the cost for a course of rTMS was not significantly different...
from that for a course of ECT as more rTMS sessions were given per course. Service costs were not different between the groups in the subsequent 6 months but informal care costs were significantly higher for the rTMS group (p = 0.04) and contributed substantially to the total cost for this group during the 6-month follow-up period. The investigators reported that there was also no difference in gain in quality adjusted life years (QALYs) for ECT and rTMS patients. The report noted that analysis of cost-effectiveness acceptability curves demonstrated that rTMS has very low probability of being more cost-effective than ECT.

The Australian Medical Services Advisory Committee (MSAC, 2007) found insufficient evidence of rTMS to support funding. The Australian MSAC considered the safety and effectiveness of rTMS for moderate to severe refractory treatment resistant depression compared to ECT and found evidence that rTMS is safe and less invasive than ECT. However, MSAC also found limited evidence that rTMS may be less effective than ECT. A more recent MSAC review reached similar conclusions (MSAC, 2014): "After considering the available evidence in relation to safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding because of uncertain effectiveness and cost-effectiveness due to insufficient comparative data in treatment-resistant patients against current antidepressant treatments and uncertain costs."

On October 8, 2008, the U.S. Food and Drug Administration (FDA) cleared for marketing via the 510(k) process the NeuroStar TMS (transcranial magnetic stimulation) Therapy system, which is specifically indicated for the treatment of major depressive disorder in adult patients who have failed to achieve satisfactory improvement from 1 prior anti-depressant medication at or above the minimal effective dose and duration in the current episode. A treatment course usually consists of 6 weeks of 40-min sessions (5 days a week). However, the evidence supporting NeuroStar’s effectiveness is less clear than its safety profile. The FDA cleared the NeuroStar based on data that found patients did modestly better when treated with TMS than when they received a sham treatment. It was a study fraught with statistical questions that concerned the agency's own scientific advisers. For a more clear answer, the National Institutes of Health has an independent study under way that tracks 260 patients (Associated Press, 2008).

Randomized, controlled studies of rTMS compared to sham treatment have produced conflicting results (O'Rearlon et al, 2007; Avery et al, 2008; Mogg et al, 2008).
In a double-blind, multi-site study, O'Reardon et al (2007) examined if TMS over the left dorsolateral prefrontal cortex (DLPFC) is effective and safe in the acute treatment of major depression. A total of 301 medication-free patients with major depression who had not benefited from prior treatment were randomized to active (n = 155) or sham TMS (n = 146) conditions. Sessions were conducted 5 times per week with TMS at 10 pulses/sec, 120 % of motor threshold, 3,000 pulses/session, for 4 to 6 weeks. Primary outcome was the symptom score change as assessed at week 4 with the Montgomery-Asberg Depression Rating Scale (MADRS). Secondary outcomes included changes on the 17- and 24-item Hamilton Depression Rating Scale (HAMD) and response and remission rates with the MADRS and HAMD. Active TMS was significantly superior to sham TMS on the MADRS at week 4 (with a post hoc correction for inequality in symptom severity between groups at baseline), as well as on the HAMD17 and HAMD24 scales at weeks 4 and 6. Response rates were significantly higher with active TMS on all 3 scales at weeks 4 and 6. Remission rates were approximately 2-fold higher with active TMS at week 6 and significant on the MADRS and HAMD24 scales (but not the HAMD17 scale). Active TMS was well-tolerated with a low drop-out rate for adverse events (4.5 %) that were generally mild and limited to transient scalp discomfort or pain. The authors concluded that TMS was effective in treating major depression with minimal side effects reported.

Avery and colleagues (2008) described the results of an open-label extension study of active TMS in medication-resistant patients with MDD who did not benefit from an initial course of therapy in a previously reported 6-week, RCT of active versus sham TMS. Patients with DSM-IV-defined MDD were actively enrolled in the study from February 2004 through September 2005 and treated with left pre-frontal TMS administered 5 times per week at 10 pulses per second, at 120 % of motor threshold, for a total of 3,000 pulses/session. The primary outcome was the baseline to endpoint change score on the MADRS. In those patients who received sham in the preceding RCT (n = 85), the mean reduction in MADRS scores after 6 weeks of open-label active TMS was -17.0 (95 % CI: -14.0 to -19.9). Further, at 6 weeks, 36 (42.4 %) of these patients achieved response on the MADRS, and 17 patients (20.0 %) remitted (MADRS score less than 10). For those patients who received and did not respond to active TMS in the preceding randomized controlled trial (n = 73), the mean reduction in MADRS scores was -12.5 (95 % CI: -9.7 to -15.4), and response and remission rates were 26.0 % and 11.0 %, respectively, after 6 weeks of additional open-label TMS treatment. The authors concluded that this open-label study provides further evidence that TMS is a safe and effective
treatment of MDD. Furthermore, continued active TMS provided additional benefit to some patients who failed to respond to 4 weeks of treatment, suggesting that longer courses of treatment may confer additional therapeutic benefit.

On the other hand, Mogg and co-workers (2008) noted that the effectiveness of rTMS for major depression is unclear. These investigators performed a RCT comparing real and sham adjunctive rTMS with 4-month follow-up. A total of 59 patients with major depression were randomly assigned to a 10-day course of either real (n = 29) or sham (n = 30) rTMS of the left DLPFC. Primary outcome measures were the 17-item HAMD and proportions of patients meeting criteria for response (50 % reduction in HAMD) and remission (HAMD8) after treatment. Secondary outcomes included mood self-ratings on Beck Depression Inventory-II and visual analog mood scales, Brief Psychiatric Rating Scale score, and both self-reported and observer-rated cognitive changes. Patients had 6-week and 4-month follow-ups. Overall, HAMD scores were modestly reduced in both groups but with no significant group x time interaction (p = 0.09) or group main effect (p = 0.85); the mean difference in HAMD change scores was -0.3 (95 % CI: -3.4 to 2.8). At end-of-treatment time-point, 32 % of the real group were responders compared with 10 % of the sham group (p = 0.06); 25 % of the real group met the remission criterion compared with 10 % of the sham group (p = 0.2); the mean difference in HAMD change scores was 2.9 (95 % CI: -0.7 to 6.5). There were no significant differences between the 2 groups on any secondary outcome measures. Blinding was difficult to maintain for both patients and raters. The authors concluded that adjunctive rTMS of the left DLPFC could not be shown to be more effective than sham rTMS for treating depression.

Demirtas-Tatlidede et al (2008) examined the impact of rTMS throughout the long course of MDD and the effectiveness of rTMS in the treatment of depressive relapses. A total of 16 medication-free patients with refractory MDD (diagnosed according to DSM-IV) who initially had clinically significant anti-depressant responses to a 10-day course of 10-Hz rTMS were consecutively admitted to the protocol from 1997 to 2001 and were followed for 4 years. The cohort was studied during a total of 64 episodes of depressive relapse. Severity of depression was evaluated with the HAMD and the BDI prior to and after completion of each rTMS treatment course. Clinically significant response was defined as a reduction in HAMD score of at least 50 %. Safety was assessed by serial neurological examinations and neuropsychological evaluations. Approximately 50 % of the patients individually sustained a clinically significant response to the repeated
courses of rTMS; the mean +/- SD decrease in HAMD scores was 64.8 % +/- 12.6 % (p < 0.0001), and, in BDI scores, 60.4 % +/- 20.6 % (p < 0.0001). Despite the lack of adjuvant anti-depressant medication, the mean interval between treatment courses was approximately 5 months, and the medication-free period ranged from 26 to 43 months. Transcranial magnetic stimulation was well-tolerated, and evaluations regarding the safety of the repeated applications of rTMS revealed no findings of concern. The authors concluded that repeated rTMS applications have demonstrated a reproducible anti-depressant effect in patients with refractory depression who initially showed a clinically significant benefit. The duration of effect varied across patients, but benefits were sustained for a mean of nearly 5 months. They stated that further studies with larger cohorts will be useful in determining the long-term effectiveness of rTMS maintenance therapy.

In a systematic review and meta-analysis, Lam and colleagues (2008) examined the effectiveness of rTMS for treatment-resistant depression (TRD). The systematic review was conducted by identifying published RCTs of active rTMS, compared with a sham control condition in patients with defined TRD (i.e., at least 1 failed trial). The primary outcome was clinical response as determined from global ratings, or 50 % or greater improvement on a rating scale. Other outcomes included remission and standardized mean differences in end point scores. Meta-analysis was conducted for absolute risk differences using random effects models. Sensitivity and subgroup analyses were also conducted to explore heterogeneity and robustness of results. A total of 24 studies (n = 1,092 patients) met criteria for quantitative synthesis. Active rTMS was significantly superior to sham conditions in producing clinical response, with a risk difference of 17 % and a number-needed-to-treat of 6. The pooled response and remission rates were 25 % and 17 %, and 9 % and 6 % for active rTMS and sham conditions, respectively. Sensitivity and subgroup analyses did not significantly affect these results. Drop-outs and withdrawals owing to adverse events were very low. The authors concluded that for patients with TRD, rTMS appears to provide significant benefits in short-term treatment studies. However, the relatively low response and remission rates, the short durations of treatment, and the relative lack of systematic follow-up studies suggested that further studies are needed before rTMS can be considered as a first-line monotherapy treatment for TRD. This is in agreement with the observations of Daskalakis and colleagues as well as Loo and associates. The former group of researchers (Daskalakis et al, 2008) stated that more studies are needed to address the current limitations of rTMS and to optimize the effectiveness of this promising therapeutic option in TRD. The latter group of investigators (Loo
et al, 2008) noted that long-term effects of repeated rTMS sessions are as yet unknown. When given within recommended guidelines, the overall safety profile of rTMS is good, and supports its further development as a clinical treatment. It is also interesting to note that Knapp and co-workers (2008) stated that ECT is more cost-effective than rTMS in the treatment of severe depression.

Demitrack and Thase (2009) studied the clinical significance of the treatment effects seen with TMS in pharmaco-resistant major depression in their recently completed studies by comparing these outcomes with the results reported in several large, comprehensive published reference data sets of anti-depressant medications studied in both treatment-responsive and treatment-resistant patient populations. The efficacy of TMS reported in RCTs was comparable to that of anti-depressants studied in similarly designed registration trials and to the adjunctive use of atypical anti-psychotic medications in controlled trials of anti-depressant non-responders. The authors noted that these data may be helpful in treatment-planning decisions when using TMS in clinical practice.

In a prospective, multi-site, randomized, active sham-controlled (1:1 randomization) trial, George et al (2010) examined if daily left pre-frontal rTMS safely and effectively treats major depressive disorder. About 860 outpatients were screened, yielding 199 anti-depressant drug-free patients with unipolar non-psychotic major depressive disorder. These researchers delivered rTMS to the left pre-frontal cortex at 120 % motor threshold (10 Hz, 4-second train duration, and 26-second intertrain interval) for 37.5 mins (3,000 pulses per session) using a figure-eight solid-core coil. Sham rTMS used a similar coil with a metal insert blocking the magnetic field and scalp electrodes that delivered matched somatosensory sensations. In the intention-to-treat sample (n = 190), remission rates were compared for the 2 treatment arms using logistic regression and controlling for site, treatment resistance, age, and duration of the current depressive episode. Patients, treaters, and raters were effectively masked. Minimal adverse effects did not differ by treatment arm, with an 88 % retention rate (90 % sham and 86 % active). Primary efficacy analysis revealed a significant effect of treatment on the proportion of remitters (14.1 % active rTMS and 5.1 % sham) (p = 0.02). The odds of attaining remission were 4.2 times greater with active rTMS than with sham (95 % CI: 1.32 to 13.24). The number needed to treat was 12. Most remitters had low anti-depressant treatment resistance. Almost 30 % of patients remitted in the open-label follow-up (30.2 % originally active and 29.6 % sham). The authors concluded
that the findings of this study suggested that daily left pre-frontal rTMS produced statistically significant and clinically meaningful anti-depressant therapeutic effects for unipolar depressed patients who are refractory to or intolerant of medications.

There are several limitations with the afore-mentioned study: (i) as a consequence of the extensive work in designing a sham system, which delayed the start of the trial, the study failed to enroll the projected 240 subjects suggested by the initial power analysis. This power issue may be the reason why the treatment condition effect on remission rate in the fully adherent sample analysis was not statistically significant. Treaters were able to guess randomization assignment better than chance, without much confidence, which was not explained by covarying for clinical benefit, (ii) although the treatment effect was statistically significant on a clinically meaningful variable (remission), the overall number of remitters and responders was less than one would like with a treatment that requires daily intervention for 3 weeks or more, and (iii) it is unclear how long the clinical benefit lasts once achieved.

Slotema et al (2010) examined if rTMS is effective for various psychiatric disorders. A literature search was performed from 1966 through October 2008 using PubMed, Ovid Medline, Embase Psychiatry, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and PsycINFO. The following search terms were used: transcranial magnetic stimulation, TMS, repetitive TMS, psychiatry, mental disorder, psychiatric disorder, anxiety disorder, attention-deficit hyperactivity disorder, bipolar disorder, catatonia, mania, depression, obsessive-compulsive disorder, psychosis, post-traumatic stress disorder, schizophrenia, Tourette's syndrome, bulimia nervosa, and addiction. Data were obtained from randomized, sham-controlled studies of rTMS treatment for depression (34 studies), auditory verbal hallucinations (AVH, 7 studies), negative symptoms in schizophrenia (7 studies), and obsessive-compulsive disorder (OCD, 3 studies). Studies of rTMS versus ECT (6 studies) for depression were meta-analyzed. Standardized mean effect sizes of rTMS versus sham were computed based on pre-treatment versus post-treatment comparisons. The mean weighted effect size of rTMS versus sham for depression was 0.55 (p < 0.001). Monotherapy with rTMS was more effective than rTMS as adjunctive to anti-depressant medication. Electro-convulsive therapy was superior to rTMS in the treatment of depression (mean weighted effect size -0.47, p = 0.004). In the treatment of AVH, rTMS was superior to sham treatment, with a mean weighted effect size of 0.54 (p < 0.001). The mean weighted effect size for rTMS versus
sham in the treatment of negative symptoms in schizophrenia was 0.39 (p = 0.11) and for OCD, 0.15 (p = 0.52). Side effects were mild, yet more prevalent with high-frequency rTMS at frontal locations. While the authors concluded that it is time to provide rTMS as a clinical treatment method for depression, for auditory verbal hallucinations, and possibly for negative symptoms, they do not recommend rTMS for the treatment of OCD. Furthermore, the authors also stated that "[a]lthough the efficacy of rTMS in the treatment of depression and AVH may be considered proven, the duration of the effect is as yet unknown. Effect sizes were measured immediately after the cessation of rTMS treatment. There are indications that the effects of rTMS may last for several weeks to months. Future studies should assess symptom relief with longer follow-up periods to assess the cost-effectiveness of rTMS treatment, and to indicate its economic advantages and disadvantages .... Although rTMS cannot replace ECT in depressive patients, there may be subgroups in which rTMS can replace antidepressant medication".

The National Institute for Health and Clinical Excellence’s interventional procedure overview of TMS for severe depression (2007) concluded that current evidence suggests there are no major safety concerns associated with TMS for severe depression, but there is no evidence that the procedure has clinically useful efficacy. Thus, TMS should be performed only in the context of research studies. Any future research should focus on factors including dose intensity, frequency and duration. Furthermore, the Institute for Clinical Systems Improvement’s guideline on major depression in adults in primary care (2008) stated that results of research studies to date on rTMS for the treatment of MDD have been inconsistent and inconclusive.

The BCBS Association’s Medical Advisory Panel (BCBSA, 2009) concluded that the use of rTMS in the treatment of depression does not meet the TEC criteria. The TEC assessment stated that an important limitation of the evidence is lack of information beyond the acute period of treatment. The TEC assessment noted that most of the clinical trials of rTMS evaluate the outcomes at the point of the last rTMS treatment, between 1 and 4 weeks, and that very few studies evaluated patients beyond this time period. Although meta-analyses are consistent with short-term antidepressant effects, the clinical significance of the effect is uncertain. The TEC assessment stated that the large clinical trial of rTMS by O’Reardon et al (2007) that was reviewed in this assessment did not unequivocally demonstrate efficacy, as the principal endpoint was not statistically significant at 4 weeks, and some results were sensitive to the methods of analysis. The TEC assessment
stated that patients in whom rTMS is indicated are usually treated with a second course of antidepressant therapy. The clinical trial by O'Reardon et al (2007), which was sham controlled without active treatment, can not determine whether rTMS would be more or less successful than this standard treatment. Referring to the study by George et al (2010), the TEC assessment also noted that a clinical trial sponsored by the National Institute of Mental Health has recruited subjects for another clinical trial of rTMS; however, this trial also appears to have only a short duration (3 weeks) in which the participants are randomized to rTMS or sham before crossovers or alternative treatments are offered.

An assessment by the California Technology Assessment Forum (CTAF, 2009) of rTMS for treatment-resistant depression concluded that rTMS does not meet CTAF technology assessment criteria. This report stated that there is insufficient evidence to conclude that rTMS improves net health outcomes for patients with treatment resistant depression, or that it is as effective as current alternatives (e.g., augmentation, ECT, or new drugs). The report noted that many of the individual studies of rTMS for treatment-resistant depression randomized less than 20 patients and were under-powered to detect changes in net health outcomes, particularly remission of depression. The CTAF assessment stated that the largest and most recent clinical trials of rTMS for depression failed to demonstrate significant improvements on their primary outcome measures. The CTAF assessment noted, in addition, that there is no consensus on how to perform rTMS and a dearth of evidence on the efficacy of rTMS after cessation of therapy. "Undoubtedly because of the evidence that treatment does have some clinical effect, there is active ongoing research into rTMS. However, it is too early to conclude that rTMS improves net health outcomes for patients with treatment resistant depression, much less that it is as effective as current alternatives such as augmentation, new drugs, or ECT."

An assessment of rTMS by the Health Council of the Netherlands (2008) stated that efficacy studies should focus, in particular, on the use of rTMS to treat patients suffering from depression who are not responding well to medication. The assessment stated that it would also be useful to study the longer term effects of rTMS therapy in depression.

An assessment of rTMS for depression by the Swedish Council on Technology Assessment in Health Care (SBU) (Brorrson et al, 2009) concluded that although the results of the studies are promising, they continue to regard the treatment as
experimental. The assessment noted that one issue is that it is not known to what extent the treatment is effective in drug-resistant depression. The assessment also called for additional studies examining potential adverse effects of rTMS on memory.

An American Psychiatric Association practice guideline on major depression (2010, reaffirmed 2015) stated: "For patients whose symptoms have not responded adequately to medication, ECT remains the most effective form of therapy and should be considered [I]. In patients capable of adhering to dietary and medication restrictions, an additional option is changing to a nonselective MAOI [II] after allowing sufficient time between medications to avoid deleterious interactions [I]. Transdermal selegiline, a relatively selective MAO B inhibitor with fewer dietary and medication restrictions, or transcranial magnetic stimulation could also be considered [II]. . . Based on the results of a multisite randomized sham-controlled clinical trial of high-frequency TMS over the left dorsolateral prefrontal cortex, TMS was cleared by the FDA in 2008 for use in individuals with major depressive disorder who have not had a satisfactory response to at least one antidepressant trial in the current episode of illness. However, another large randomized sham-controlled trial of TMS added to antidepressant pharmacotherapy showed no significant benefit of left dorsolateral prefrontal cortex TMS. In comparisons of actual TMS versus sham TMS, most but not all recent meta-analyses have found relatively small to moderate benefits of TMS in terms of clinical response. Although the primary studies used in these meta-analyses are highly overlapping and the variability in TMS stimulus parameters and treat treatment paradigms complicates the interpretation of research findings, these meta-analyses also support the use of high-frequency TMS over the left dorsolateral prefrontal cortex. Lesser degrees of treatment resistance may be associated with a better acute response to TMS. In comparison with ECT, TMS has been found in randomized studies to be either less effective than ECT or comparable in efficacy to ECT, but in the latter studies TMS was more effective and ECT was less effective than is typically seen in clinical trials. A fewer number of studies have compared cognitive effects of TMS and ECT. One randomized trial found no significant difference between TMS and non-dominant unilateral ECT on performance on neuropsychological tests at 2 and at 4 weeks of treatment, although a small open-label trial reported a greater degree of memory difficulties with ECT than with TMS shortly after the treatment course."
In a review on “Transcranial magnetic stimulation in the management of mood disorders”, Allan et al (2011) presented an up-to-date meta-analysis of TMS in the treatment of depression. These investigators searched Medline and Embase from 1996 until 2008 for randomized sham-controlled trials, with patients and investigators blinded to treatment, and outcome measured using a version of the Hamilton Depression Rating Scale (or similar). They identified 1,789 studies; 31 were suitable for inclusion, with a cumulative sample of 815 active and 716 sham TMS courses. These researchers found a moderately sized effect in favor of TMS [Random Effects Model Hedges’ g = 0.64, 95 % CI: 0.50 to 0.79]. The corresponding Pooled Peto Odds Ratio for treatment response (less than or equal to 50 % reduction in depression scores) was 4.1 (95 % CI: 2.9 to 5.9). There was significant variability between study effect sizes. Meta-regressions with relevant study variables did not reveal any predictors of treatment efficacy. A total of 9 studies included follow-up data with an average follow-up time of 4.3 weeks; there was no mean change in depression severity between the end of treatment and follow-up (Hedges’ g = -0.02, 95 % CI: -0.22 to +0.18) and no heterogeneity in outcome. The authors concluded that TMS appears to be an effective treatment; however, at 4 weeks’ follow-up after TMS, there had been no further change in depression severity. Problems with finding a suitably blind and ineffective placebo condition may have confounded the published effect sizes. If the TMS effect is specific, only further large double-blind RCTs with systematic exploration of treatment and patient parameters will help to define optimum treatment indications and regimen.

The BlueCross BlueShield Technology Evaluation Center (TEC)’s assessment on TMS for depression (2011) concludes that “[t]he available evidence does not permit conclusions regarding the effect of TMS on health outcomes or compared with alternatives. Comparison to alternatives using other observational studies may not be valid due to unmeasured differences in severity of depression between studies and other differences in studies”. It also states that “the current body of evidence can not determine in a rigorous way whether TMS would be as effective as a second course of antidepressant therapy. Other important gaps in current knowledge include whether TMS is effective as an adjunctive treatment to second-line drug therapy, the durability of TMS treatment, and the effectiveness of retreatment”.

An Agency for Healthcare Research and Quality's review (Gaynes et al, 2011) reported that there is insufficient evidence to evaluate whether non-
pharmacological treatments are effective for TRD. The review summarized evidence of the effectiveness of 4 non-pharmacological treatments: (i) ECT, (ii) rTMS, (iii) VNS, and (iv) cognitive behavioral therapy (CBT) or inter-personal psychotherapy. With respect to maintaining remission (or preventing relapse), there were no direct comparisons (evidence) involving ECT, rTMS, VNS, or CBT. With regard to indirect evidence, there were 3 fair trials compared rTMS with a sham procedure and found no significant differences, however, too few patients were followed during the relapse prevention phases in 2 of the 3 studies (20-week and 6-month follow-up) and patients in the 3rd study (3-month follow-up) received a co-intervention providing insufficient evidence for a conclusion. There were no eligible studies for ECT, VNS, or psychotherapy. The review concluded that that comparative clinical research on non-pharmacologic interventions in a TRD population is early in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data is substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS. However, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for benefits, reflecting low confidence that the evidence reflects the true effect and indicating that further research is likely to change our confidence in these findings. This finding of low strength is most notable in 2 cases: ECT and rTMS did not produce different clinical outcomes in TRD, and ECT produced better outcomes than pharmacotherapy. No trials directly compared the likelihood of maintaining remission for non-pharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between non-pharmacologic interventions. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing non-pharmacologic interventions with themselves and with pharmacologic treatments, and to delineate carefully the number of treatment failures following a treatment attempt of adequate dose and duration in the current episode.

Using data from the AHRQ report, the Institute for Clinical and Economic Review (ICER, 2011) conducted a cost-effectiveness modeling study, assuming that transcranial electrical stimulation and electroconvulsive therapy have equivalent efficacy. The model predicted a cost-utility ratio of $216,468 per quality adjusted life year from a payer perspective and $321,880 per quality adjusted life year from a societal perspective.
An assessment by the University of Calgary Health Technology Assessment Unit (Leggett, et al., 2014) stated that, in adults with TRD, rTMS is more effective than no treatment but the optimal protocol remains unclear. The assessment found that few studies have reported on the effectiveness of rTMS compared to ECT. The assessment stated that pooled estimates for response and remission provide conflicting results indicating rTMS may be more effective at achieving response but less effective at achieving remission. The assessment concluded that the effectiveness of rTMS compared to ECT remains unclear. The assessment also concluded that the effectiveness in youth and young adult populations is uncertain.

An assessment by the Galacian Health Technology Assessment Agency (AVALIA-T, 2014) reached similar conclusions: "Transcranial magnetic stimulation is not currently recommended as a treatment for depression, due to uncertainty about its clinical efficacy."

An assessment by the Alberta Health Technology Assessment Unit (2014) concluded that, in adults with treatment resistant depression, repetitive transcranial magnetic stimulation is more effective than no treatment but the optimal protocol remains unclear. No statistically significant differences were found between repetitive transcranial magnetic stimulation and electroconvulsive therapy; it is unclear which is most efficacious. The assessment also found that the effectiveness in youth and young adult populations is uncertain.

Hayes (2014) reported on a metaanalysis of controlled trials of TMS with sham stimulation. Most studies required patients to have 1 or more, and most typically two or more, previously failed trials of antidepressant medication. The post-treatment difference between transcranial magnetic stimulation and sham stimulation favored TMS; most differences were reported to be statistically significant, but the magnitude was generally small as measured by the MADRS scale and the various HAMD scales. No standard definition of clinically relevant improvement or a clinically relevant effect was identified in the literature. There is evidence of a strong placebo effect. A small quantity of data suggested that the durability of effect, i.e., the continued advantage of active transcranial magnetic stimulation over sham transcranial magnetic stimulation, may not last beyond 2 or 3 weeks after the end of treatment. Low quality evidence suggested that transcranial magnetic stimulation may be at least as effective as electroconvulsive therapy under certain circumstances, but under other circumstances, electroconvulsive may be superior; this evidence is of low quality because of unexplained inconsistency in
study results. Low quality evidence suggested that if transcranial magnetic stimulation has any effect on quality of life or function, it is very small. The review found insufficient evidence on the use of transcranial magnetic stimulation as maintenance therapy after acute response.

An assessment by the BlueCross BlueShield Association Technology Evaluation Center (BCBSA, 2014) concluded that transcranial magnetic stimulation for depression does not meet the TEC criteria. The assessment stated that “adequately powered trials do not provide convincing evidence of improved health outcomes.” The assessment noted that meta-analyses included a large number of trials, but their pooled results do not change the conclusions drawn from the large trials. The authors of the TEC assessment found that short-term randomized comparisons from 3 trials (2 reporting adequate power to detect effects and the third trial similar in size) do not provide consistent evidence that TMS improves remission of major depressive disorder compared with a sham procedure in patients failing 1 or more antidepressant trials. The authors stated that comparisons reported beyond the initial treatment period (3 weeks of TMS) in 2 of the trials (O'Reardon et al. 2007; George et al. 2010) are problematic given the planned crossover and dropouts. Analyses that take into account potential confounding introduced by crossovers were not reported. The assessment found no evidence comparing TMS with changing antidepressant or augmentation similar to the strategy employed in the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study (Rush et al. 2006).

The TEC assessment included meta-analyses published from 2010 through the search date and trials enrolling more than 150 patients. The quality of meta-analyses was appraised using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) criteria. Randomized controlled trial quality was assessed using the U.S. Preventive Services Task Force criteria. Three randomized, controlled trials were identified that met inclusion criteria. Results from 2 trials were published at the time of the assessment -- George, et al. (2010) and O'Reardon, et al. (2007) -- and documents submitted to the FDA for the Brainsway device (subsequently published as Levkovitz, et al., 2015). The 2 published trials employed a so-called “duration adaptive design” or “forced dropout strategy” after 3 weeks of active TMS or sham. The TEC assessment rated trial quality separately for results after 3 and 6 weeks of TMS: O'Reardon et al. (2007) was rated fair at 3 weeks and poor at 6 weeks. Response rates at three weeks for TMS versus sham were 20.6 percent and 11.6 percent at three weeks, which was statistically
significant; however, the differences in remission rates at three weeks between TMS and sham were not statistically significant. There was also no statistically significant difference in remission rates at six weeks. George et al. (2010) was rated good at 3 weeks and poor at 6 weeks. There was no statistically significant difference in remission rates between TMS and sham at three weeks. Although statistically significant differences in response and remission rates were reported at six weeks, trial quality for the 6-week results was rated poor because of crossover and dropouts during the second 3 weeks of treatment. Limited data are available from the Brainsway device trial that assessed outcomes at 4 and 16 weeks. Although there were significant differences between TMS and sham in per protocol and "modified intention to treat" analyses, treatment differences between TMS and sham in the intention-to-treat (ITT) analysis were not significantly different.

The BlueCross BlueShield Assessment (2014) also looked at the result of the extension studies, finding that the response rates seen in the extension studies were difficult to interpret given the open-label nature of treatment and the lack of randomized comparator. Longer-term follow-up was examined in extension studies to the O’Reardon et al. (2007) and George et al. (2010) trials as well as in the meta-analysis by Allan et al. (2011). Patients in the O’Reardon et al. trial who did not respond (both active TMS and sham) were allowed to participate in an additional 6 weeks of repetitive TMS. The response and remission rates improved for both groups, and these outcome improvements occurred more frequently in the extension phase than in the original randomization phase. Another extension of this trial followed responders from either the initial randomized trial or the extension study above. Participants were followed 12 weeks for recurrence or additional TMS treatments, with a relapse rate of 12.9% with additional TMS treatment in 40.6%. The extension study to the George et al. (2010) trial enrolled 141 patients who failed to achieve remission in the original randomized phase of the trial. These participants were given additional TMS treatment for 6 weeks, but the TEC assessment noted that these results are difficult to interpret because the study lacked a control group. Any participant who remitted in the original trial or the extension study was eligible for inclusion into the third phase of the trial. Fifty patients underwent repetitive TMS tapering and were followed for 3 months. By the end of follow-up, 29 (58%) maintained remission, 2 (4%) were reclassified as partial responders, and 1 (2%) relapsed. The TEC assessment stated that the study’s unblinded, nonrandomized design and high loss to follow-up prevent any conclusions about the efficacy of repetitive TMS. The TEC assessment concluded that, because of the lack of demonstrable efficacy in the randomized comparisons,
the results of the longer follow-ups reported in O’Reardon et al. (O’Reardon et al. 2007) and George et al. (George et al. 2010) offer little toward establishing treatment benefit. The TEC assessment stated that the higher response rates seen in the extension studies are difficult to interpret given the open-label nature of treatment and lack of randomized comparator.

The TEC assessment identified concerns about publication bias affecting the conclusions of the metaanalyses. Seven meta-analyses published in 2010 or later were identified. The 4 largest meta-analyses included between 24 and 34 trials. Besides differing by year of publication and available studies, the meta-analyses applied different selection criteria and analytic approaches. All meta-analyses examined clinical end points at the conclusion of TMS treatment (i.e., 1 to 5 weeks). Limited evidence on the durability of outcomes was reported in 1 analysis. The meta-analyses concluded that repetitive TMS is superior to sham for treating medication-resistant depression over the short term, and possibly over a longer term. A single meta-analysis satisfied all AMSTAR criteria, and it was the only analysis to assess trial quality (risk of bias). One meta-analysis suggested a possibility of publication bias, others did not report examining potential publication bias, and some found no indication to suspect it. A large majority of trials were small, and there was considerable overlap among the trials included in the meta-analyses. The only meta-analysis to satisfy all AMSTAR criteria included the 6-week results from O’Reardon et al. (2007), and it was conducted prior to the availability of the Brainsway results. The TEC assessment was unable to identify published results for 11 completed trials registered on ClinicalTrials.gov; the published evidence is incomplete. Concerns by the authors of the TEC assessment about conclusions from the meta-analyses center on the potential for publication bias, and inclusion of the problematic 6-week results from 2 trials. The TEC assessment stated that the three adequately powered trials do not provide convincing evidence of improved health outcomes. The meta-analyses included a large number of trials, but their pooled results do not change the conclusions drawn from the large adequately powered trials. The TEC assessment stated that, although durability of any effects is relevant, absent demonstrable benefit compared with a sham, the question is of lesser or even little importance.
An assessment by the Canadian Agency for Drugs and Technologies in Health (CADTH, 2014) stated that some studies of transcranial magnetic stimulation may show a benefit, but four health technology assessments have been unable to make conclusions. The assessment concluded that “evidence is generally inconsistent and of low quality.”

Dunner and colleagues (2014) evaluated the long-term effectiveness of TMS in naturalistic clinical practice settings following acute treatment for patients not benefiting from antidepressants. Adult patients with a primary diagnosis of unipolar, non-psychotic major depressive disorder (DSM-IV clinical criteria), who did not benefit from antidepressant medication, received TMS treatment in 42 clinical practices. A total of 257 patients completed a course of acute TMS treatment and consented to follow-up over 52 weeks. Assessments were obtained at 3, 6, 9, and 12 months. The study was conducted between March 2010 and August 2012. Compared with pre-TMS baseline, there was a statistically significant reduction in mean total scores on the Clinical Global Impressions-Severity of Illness scale (primary outcome), 9-Item Patient Health Questionnaire, and Inventory of Depressive Symptoms-Self Report (IDS-SR) at the end of acute treatment (all p < 0.0001), which was sustained throughout follow-up (all p < 0.0001). The proportion of patients who achieved remission at the conclusion of acute treatment remained similar at conclusion of the long-term follow-up. Among 120 patients who met IDS-SR response or remission criteria at the end of acute treatment, 75 (62.5 %) continued to meet response criteria throughout long-term follow-up. After the first month, when the majority of acute TMS tapering was completed, 93 patients (36.2 %) received re-introduction of TMS. In this group, the mean (SD) number of TMS treatment days was 16.2 (21.1). The authors concluded that TMS demonstrated a statistically and clinically meaningful durability of acute benefit over 12 months of follow-up. This was observed under a pragmatic regimen of continuation antidepressant medication and access to TMS retreatment for symptom recurrence. The main drawbacks of this study were: (i) its observational, naturalistic design (no concurrent control group), (ii) conclusions regarding the influence of concomitant treatments, including the role of TMS re-introduction, cannot be fully explored, and (iii) analysis using an LOCF (last-observation-carried-forward) analysis method may exaggerate the consistency of the scores.

under set terms. Two authors reviewed each article and came to consensus on the inclusion and exclusion criteria. All eligible studies were reviewed, duplicates were removed, and data were extracted individually. The search identified 1,673 articles, 41 of which met both inclusion and exclusion criteria. Various biological factors at baseline appear to predict response to rTMS, including levels of certain molecular factors, blood flow in brain regions implicated in depression, electrophysiological findings, and specific genetic polymorphisms. The authors concluded that significant methodological variability in rTMS treatment protocols limited the ability to generalize conclusions. However, response to treatment may be predicted by baseline frontal lobe blood flow, and presence of polymorphisms of the 5-hydroxytryptamine (5-HT) -1a gene, the LL genotype of the serotonin transporter linked polymorphic region (5-HTTLPR) gene, and Val/Val homozygotes of the brain-derived neurotrophic factor (BDNF) gene.

Noda et al (2015) systematically synthesized the literature on the neurobiological mechanisms of treatment response to rTMS in patients with depression. Medline (1996 to 2014), Embase (1980 to 2014) and PsycINFO (1806 [???] to 2014) were searched under set terms. Three authors reviewed each article and came to consensus on the inclusion and exclusion criteria. All eligible studies were reviewed, duplicates were removed, and data were extracted individually. Of 1,647 articles identified, 66 studies met both inclusion and exclusion criteria; rTMS affects various biological factors that can be measured by current biological techniques. Although a number of studies have explored the neurobiological mechanisms of rTMS, a large variety of rTMS protocols and parameters limited the ability to synthesize these findings into a coherent understanding. However, a convergence of findings suggested that rTMS exerts its therapeutic effects by altering levels of various neurochemicals, electrophysiology as well as blood flow and activity in the brain in a frequency-dependent manner. The authors concluded that more research is needed to delineate the neurobiological mechanisms of the antidepressant effect of rTMS. The incorporation of biological assessments into future rTMS clinical trials will help in this regard.

Serafini et al (2015) performed a systematic review of the current literature (PubMed/Medline, Scopus and ScienceDirect search) to examine the role of rTMS in improving neuro-cognition in patients with treatment-resistant depression (TRD). Studies were included according to the following criteria: (i) being an original paper in a peer-reviewed journal, and (ii) having analyzed the effect of rTMS on neurocognitive functioning in TRD.
The combined search strategy yielded a total of 91 articles, of which, after a complete analysis, 22 fulfilled the inclusion criteria. Based on the main findings, most of the selected studies suggested the existence of a trend towards improvements in the neurocognitive profile using rTMS. Negative findings have also been reported. However, most studies were limited by their small sample size or included mixed samples, or the adopted single-blind designs potentially biased the blinding of the study design. The authors concluded that rTMS is a non-invasive brain stimulation that may be considered a valuable and promising technique for cognitive enhancement in TRD.

In an open-label study, McGirr et al (2015) the effectiveness and acceptability of an accelerated rTMS protocol for major depressive disorder (MDD). In this naturalistic trial, 27 patients with moderate-to-severe chronic and treatment-resistant MDD were treated with twice-daily HF-rTMS (10 Hz) applied over the left dorsolateral prefrontal cortex for 2 consecutive weeks (60,000 pulses). The primary outcomes were rates of clinical remission and response (16-item Quick Inventory of Depressive Symptomatology post-treatment score less than or equal to 6, and greater than or equal to 50 % reduction, respectively). Secondary outcomes were self-reported anxious symptoms, depressive symptoms and quality of life, and dropout rates as a proxy for acceptability. A total of 10 (37.0 %) patients met criteria for clinical remission and 15 (55.6 %) were classified as responders, with comparable outcomes for both moderate and severe MDD. Clinician-rated improvements in depressive symptoms were paralleled in self-reported depressive and anxious symptoms, as well as quality of life. No patient discontinued treatment. The authors concluded that an accelerated protocol involving twice-daily sessions of HF-rTMS over the left DLPFC for 2 weeks was effective in treatment-resistant MDD, and had excellent acceptability. They stated that additional research is needed to optimize accelerated rTMS treatment protocols and determine effectiveness using sham-controlled trials. The main drawbacks of this study were: (i) short treatment duration that might be lengthened with corresponding improvements in effectiveness, (ii) limited duration of follow-up, (iii) small sample size, and (iv) an open-label design requiring randomized controlled replication.

Rapinesi and colleagues (2015) examined the role of deep TMS (dTMS) maintenance sessions in protecting patients with bipolar disorder (BD) or recurrent MDD from developing depressive or manic relapses in a 12-month follow-up period. A total of 24 drug-resistant patients with a current depressive episode and a
diagnosis of MDD or BD were enrolled in the study. All the participants underwent daily dTMS sessions for 4 weeks. One group (maintenance -- M group) received additional maintenance dTMS sessions weekly or twice-weekly. After the 1st dTMS cycle, a significant reduction of HDRS scores was observed in all participants. Subsequently, the HDRS mean scores did not significantly change over time in the M group, while it significantly increased in the non-M-group after 6 and 12 months. The authors concluded that the findings of this study confirmed previous evidence of a positive therapeutic effect of dTMS on depressive symptoms and suggested that, after recovery from acute episodes, maintenance dTMS sessions may be helpful in maintaining euthymia in a 12-month follow-up period. The major drawbacks of this study were: (i) its open design, (ii) small sample size (n = 24), (iii) a possible confounding effect of add-on medication, (iv) the lack of a sham control, and (v) the population heterogeneity. Moreover, these researchers stated that their results should be considered as preliminary; future studies should use larger and more homogeneous samples with double-blind to better evaluate the potential effectiveness of dTMS in the treatment and the prevention of depressive episodes in mood disorders.

Lefkovitz and associates (2015) noted that dTMS is a new technology allowing non-surgical stimulation of relatively deep brain areas. In a double-blind, randomized controlled, multi-center study, these investigators evaluated the safety and effectiveness of dTMS in MDD. They recruited 212 MDD outpatients, aged 22 to 68 years, who had either failed 1 to 4 anti-depressant trials or not tolerated at least 2 anti-depressant treatments during the current episode. They were randomly assigned to monotherapy with active or sham dTMS. A total of 20 sessions of dTMS (18 Hz over the prefrontal cortex) were applied during 4 weeks acutely, and then bi-weekly for 12 weeks. Primary and secondary effectiveness end-points were the change in the HDRS-21 score and response/remission rates at week 5, respectively. Deep TMS induced a 6.39 point improvement in HDRS-21 scores, while a 3.28 point improvement was observed in the sham group (p = 0.008), resulting in a 0.76 effect size. Response and remission rates were higher in the dTMS than in the sham group (response: 38.4 % versus 21.4 %, p = 0.013; remission: 32.6 % versus 14.6 %, p = 0.005). These differences between active and sham treatment were stable during the 12-week maintenance phase. The authors concluded that dTMS was associated with few and minor side effects apart from one seizure in a patient where a protocol violation occurred. They stated that these results suggested that dTMS constitutes a novel intervention in MDD, which is safe and effective in patients not responding to anti-depressant medications, and
whose effect remains stable over 3 months of maintenance treatment. The major
drawbacks of this study were: (i) 14.6 % of the intention-to-treat analysis set were
not treated at the stimulation intensity defined by the protocol and had to be
excluded from the PP analysis. This was presumably due to the flexibility of the
operator in titrating stimulation intensity from 100 % up to 120 % of individual
motor threshold in order to improve tolerability. Thus, patients were more
likely to stay at an intensity below the optimal level compared to trials where
rTMS was defined at a fixed intensity after a brief lead-in period. The
importance of adequate intensity (120 % of individual motor threshold) should
be highly emphasized when training operators to use this system for anti­
depressant treatment, as lower intensity does not allow stimulation of deep
prefrontal cortex areas and is therefore less likely to produce the desired
clinical response, (ii) patients with psychotic depression were excluded from
the study. This decision was based on a previous trial that demonstrated the
superiority of electro-convulsive therapy to rTMS in this patient group.

However, it cannot be ruled out that psychotic patients may benefit from dTMS
treatment, particularly if it is administered concomitantly with anti-psychotic
medication, and (iii) in the present study patients were withdrawn from anti­
depressant medications prior to dTMS as required by regulatory authorities.
However, in a real-life clinical setting, anti-depressant medication that leads to a
partial response might be augmented with dTMS.

Philip et al (2016a) stated that current treatment options for post-traumatic stress
disorder (PTSD) offer modest benefits, underscoring the need for new treatments.
Repetitive transcranial magnetic stimulation depolarizes neurons in a targeted brain
region with magnetic fields typically pulsed at low (1 Hz) or high (10 Hz) frequency
to relieve MDD. Prior work suggested an intermediate pulse frequency, 5 Hz, is
also effective for treating co-morbid depressive and anxiety symptoms. In this chart
review study, these researchers systematically examined the clinical and safety
outcomes in 10 patients with co-morbid MDD and PTSD syndromes who received
5-Hz rTMS therapy at the Providence VA Medical Center Neuromodulation Clinic.
Self-report scales measured illness severity prior to treatment, after every 5
treatments, and upon completion of treatment. Results showed significant
reduction in symptoms of PTSD (p = 0.003, effect size = 1.12, 8/10 with reliable
change) and MDD (p = 0.005, effect size = 1.09, 6/10 with reliable change). The
authors concluded that stimulation was well-tolerated and there were no serious
adverse events. They stated that these data indicated 5-Hz rTMS may be a useful option to treat these co-morbid disorders; larger, controlled trials are needed to confirm the benefits of 5-Hz protocols observed in this pilot study.

Health Quality Ontario’s systematic review and meta-analysis on “Repetitive transcranial magnetic stimulation for treatment-resistant depression” (2016) examined the anti-depressant effectiveness of rTMS in patients with treatment-resistant unipolar depression. A literature search was performed for RCTs published from January 1, 1994, to November 20, 2014. The search was updated on March 1, 2015. Two independent reviewers evaluated the abstracts for inclusion, reviewed full texts of eligible studies, and abstracted data. Meta-analyses were conducted to obtain summary estimates. The primary outcome was changes in depression scores measured by the HRSD, and these researchers considered, a priori, the mean difference of 3.5 points to be a clinically important treatment effect. Remission and response to the treatment were secondary outcomes, and these investigators calculated number needed to treat on the basis of these outcomes. They examined the possibility of publication bias by constructing funnel plots and by Begg's and Egger's tests. A meta-regression was undertaken to examine the effect of specific rTMS technical parameters on the treatment effects. A total of 23 RCTs compared rTMS with sham, and 6 RCTs compared rTMS with ECT. Trials of rTMS versus sham showed a statistically significant improvement in depression scores with rTMS (weighted mean difference [WMD] 2.31, 95 % CI: 1.19 to 3.43; p < 0.001). This improvement was smaller than the pre-specified clinically important treatment effect. There was a 10 % absolute difference between rTMS and sham in the rates of remission or response. This translated to a number needed to treat of 10. Risk ratios for remission and response were 2.20 (95 % CI: 1.44 to 3.38, p = 0.001) and 1.72 (95 % CI: 1.13 to 2.62, p = 0.01), respectively, favoring rTMS. No publication bias was detected. Trials of rTMS versus ECT showed a statistically and clinically significant difference between rTMS and ECT in favor of ECT (WMD 5.97, 95 % CI: 0.94 to 11.0, p = 0.02). Risk ratios for remission and response were 1.44 (95 % CI: 0.64 to 3.23, p = 0.38) and 1.72 (95 % CI: 0.95 to 3.11, p = 0.07), respectively, favoring ECT. The authors concluded that overall, the body of evidence favored ECT for treatment of patients who are treatment-resistant; rTMS had a small short-term effect for improving depression in comparison with sham, but follow-up studies did not show that the small effect will continue for longer periods. The meta-analysis showed a positive, short-term effect. However, the issue is that the larger trials,
which is the point that the BCBS TEC assessment made, failed to reach statistical
significance on intention to treat analysis, and there was a suggestion of publication
bias with the smaller trials.

An assessment by the National Institute for Health and Care Excellence (NICE, 2015) concluded that the evidence on repetitive transcranial magnetic stimulation for depression shows no major safety concerns, and that the evidence on its efficacy in the short-term is adequate, although the clinical response is variable. The NICE assessment found little data on efficacy in the long-term. The assessment stated that, during the consent process, clinicians should, in particular, inform patients about the other treatment options available, and make sure that patients understand the possibility the procedure may not give them benefit. The NICE assessment cited the need for publication of further evidence on patient selection, details of the precise type and regime of stimulation used, the use of maintenance treatment and long-term outcomes.

Chronic Pain Syndromes

There is also a lack of scientific evidence in the use of TMS as a diagnostic tool for psychiatric disorders, and treatment for chronic pain. Pridmore et al (2005) stated that in studies of TMS for the treatment of chronic pain, there is some evidence that temporary relief can be achieved in a proportion of sufferers. Work to this point is encouraging, but systematic assessment of stimulation parameters is necessary if TMS is to attain a role in the treatment of chronic pain. Furthermore, Canavero and Bonicalzi (2005) noted that TMS has no role in the management of patients with central pain, a major chronic pain syndrome.

In a double-blind, randomized, cross-over study, Andre-Obadia et al (2008) evaluated, against placebo, the pain-relieving effects of high-rate rTMS on neuropathic pain (n = 28). The effect of a change in coil orientation (postero-anterior versus latero-medial) on different subtypes of neuropathic pain was further tested in a subset of 16 patients. Pain relief was evaluated daily during 1 week. High-frequency, postero-anterior rTMS decreased pain scores significantly more than placebo. Postero-anterior rTMS also out-matched placebo in a score combining subjective (pain relief, quality of life) and objective (rescue drug intake) criteria of treatment benefit. Changing the orientation of the coil from postero-anterior to latero-medial did not yield any significant pain relief. The analgesic effects of postero-anterior rTMS lasted for approximately 1 week. The pain-
relieving effects were observed exclusively on global scores reflecting the most distressing type of pain in each patient. Conversely, rTMS did not modify specifically any of the pain subscores that were separately tested (ongoing, paroxysmal, stimulus-evoked, or disesthesic pain). The authors concluded that postero-anterior rTMS was more effective than both placebo and latero-medial rTMS. When obtained, pain relief was not specific of any particular submodality, but rather reduced the global pain sensation whatever its type. Moreover, they stated that these findings were driven from a small number of subjects; thus they need to be replicated.

Plow and associates (2012) stated that chronic neuropathic pain is one of the most prevalent and debilitating disorders. Conventional medical management, however, remains frustrating for both patients and clinicians owing to poor specificity of pharmacotherapy, delayed onset of analgesia and extensive side effects. Neuromodulation presents as a promising alternative, or at least an adjunct, as it is more specific in inducing analgesia without associated risks of pharmacotherapy. These investigators discussed common clinical and investigational methods of neuromodulation. Compared to clinical spinal cord stimulation, investigational techniques of cerebral neuromodulation, both invasive (DBS and motor cortical stimulation [MCS]) and non-invasive (rTMS and tDCS), may be more advantageous. By adaptively targeting the multi-dimensional experience of pain, subtended by integrative pain circuitry in the brain, including somatosensory and thalamo-cortical, limbic and cognitive, cerebral methods may modulate the sensory-discriminative, affective-emotional and evaluative-cognitive spheres of the pain neuromatrix. Despite promise, the current state of results alludes to the possibility that cerebral neuromodulation has thus far not been effective in producing analgesia as intended in patients with chronic pain disorders. These techniques, thus, remain investigational and off-label. These investigators discussed issues implicated in inadequate efficacy, variability of responsiveness, and poor retention of benefit, while recommending design and conceptual refinements for future trials of cerebral neuromodulation in management of chronic neuropathic pain.

Leung et al (2009) performed a meta-analysis on the analgesic effect of rTMS on various neuropathic pain states based on their neuroanatomical hierarchy. Available RCTs were screened. Pooled individual data (PID) were coded for age, gender, pain neuroanatomical origins, pain duration, and treatment parameters analyses. Coded pain neuroanatomical origins consist of peripheral nerve (PN); nerve root (NR); spinal cord (SC); trigeminal nerve or ganglion (TGN); and post-
stroke supra-spinal related pain (PSP). Raw data of 149 patients were extracted from 5 (1 parallel, 4 cross-over) selected (from 235 articles) RCTs. A significant (p < 0.001) overall analgesic effect (mean percent difference in pain visual analog scale (VAS) score reduction with 95 % CI) was detected with greater reduction in VAS with rTMS in comparison to sham. Including the parallel study (Khedr et al), the TGN subgroup was found to have the greatest analgesic effect (28.8 %), followed by PSP (16.7 %), SC (14.7 %), NR (10.0 %), and PN (1.5 %). The results were similar when these researchers excluded the parallel study with the greatest analgesic effect observed in TGN (33.0 %), followed by SC (14.7 %), PSP (10.5 %), NR (10.0 %), and PN (1.5 %). In addition, multiple (versus single, p = 0.003) sessions and lower (greater than 1 and less than or equal to 10 Hz) treatment frequency range (versus greater than 10 Hz) appears to generate better analgesic outcome. In short, rTMS appears to be more effective in suppressing centrally than peripherally originated neuropathic pain states. The authors stated that this was the first PID-based meta-analysis to assess the differential analgesic effect of rTMS on neuropathic pain based on the neuroanatomical origins of the pain pathophysiology and treatment parameters. The derived information serves as a useful resource in regards to treatment parameters and patient population selection for future rTMS-pain studies.

Lindholm and colleagues (2015) examined the effects of rTMS in neuropathic orofacial pain, and compared 2 cortical targets against placebo. Furthermore, as dopaminergic mechanisms modulate pain responses, these researchers assessed the influence of the functional DRD2 gene polymorphism (957C>T) and the catechol-O-methyl-transferase (COMT) Val158Met polymorphism on the analgesic effect of rTMS. A total of 16 patients with chronic drug resistant neuropathic orofacial pain participated in this randomized, placebo controlled, cross-over study. Navigated high-frequency rTMS was given to the sensorimotor (S1/M1) and the right secondary somatosensory (S2) cortices. All subjects were genotyped for the DRD2 957C>T and COMT Val158Met polymorphisms. Pain, mood and quality of life were monitored throughout the study. The numerical rating scale pain scores were significantly lower after the S2 stimulation than after the S1/M1 (p = 0.0071) or the sham (p = 0.0187) stimulations. The Brief Pain Inventory scores were also lower 3 to 5 days after the S2 stimulation than at pre-treatment baseline (p = 0.0127 for the intensity of pain and p = 0.0074 for the interference of pain) or after the S1/M1 (p = 0.001 and p = 0.0001) and sham (p = 0.0491 and p = 0.0359) stimulations. No correlations were found between the genetic polymorphisms and
the analgesic effect in the present small clinical sample. The authors concluded that the right S2 cortex is a promising new target for the treatment of neuropathic orofacial pain with high-frequency rTMS.

Jin and colleagues (2015) stated that the optimal parameters of rTMS (stimulation frequency and treatment sessions) for achieving long-term analgesic effects remain unknown. These investigators evaluated the optimal parameters of rTMS for neuropathic pain (NP), including the rTMS sessions needed for inducing acute as well as long-term analgesic effects. They performed a meta-analysis of the analgesic effect of high frequency rTMS (HF-rTMS) for neuropathic patients. This meta-analysis examined all studies involving the analgesic effectiveness of HF-rTMS for NP. PubMed, Embase, and the Cochrane library were searched for clinical studies of rTMS treatment on NP published before December 31, 2014.

Crude SMD with 95% CI were calculated for pain intensity after different treatment sessions (from 1 to 10) and follow-up of 1 or 2 months after rTMS treatment using random effect models. A total of 25 studies (including 32 trials and 589 patients) were selected for the meta-analysis according to the inclusion and exclusion criteria. All 3 HF-rTMS treatments (5, 10, and 20 Hz) produced pain reduction, while there were no differences between them, with the maximal pain reduction found after 1 and 5 sessions of rTMS treatment. Further, this significant analgesic effect remained for 1 month after 5 sessions of rTMS treatment. The authors concluded that HF-rTMS stimulation on primary motor cortex is effective in relieving pain in NP patients. Although 5 sessions of rTMS treatment produced a maximal analgesic effect and may be maintained for at least 1e month, further large-scale and well-controlled trials are needed to determine if this enhanced effect is specific to certain types of NP such as post-stroke related central NP. There main drawbacks of this meta-analysis were: (i) the long-term analgesic effects of different HF-rTMS and low frequency (LF) rTMS sessions, including the single session of rTMS on different NP of varying origins have yet not been evaluated, and (ii) the full degree of pain relief is still unclear for many rTMS studies.

Mulla et al (2015) noted that central post-stroke pain is a chronic neuropathic disorder that follows a stroke. Current research on its management is limited, and no review has evaluated all therapies for central post-stroke pain. These investigators conducted a systematic review of RCTs to evaluate therapies for central post-stroke pain. They identified eligible trials, in any language, by systematic searches of AMED, CENTRAL, CINAHL, DARE, EMBASE, HealthSTAR, MEDLINE, and PsychINFO. Eligible trials; (i) enrolled greater than or
equal to 10 patients with central post-stroke pain; (ii) randomly assigned them to an active therapy or a control arm; and (iii) collected outcome data greater than or equal to 14 days after treatment. Pairs of reviewers, independently and in duplicate, screened titles and abstracts of identified citations, reviewed full texts of potentially eligible trials, and extracted information from eligible studies. These researchers used a modified Cochrane tool to evaluate risk of bias of eligible studies, and collected patient-important outcomes according to recommendations by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. They conducted, when possible, random effects meta-analyses, and evaluated the certainty in treatment effects using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) System. A total of 8 eligible English language RCTs (459 patients) tested anti-convulsants, an anti-depressant, an opioid antagonist, rTMS, and acupuncture. Results suggested that all therapies had little to no effect on pain and other patient-important outcomes. The certainty in the treatment estimates ranged from very low to low. The authors concluded that these findings were inconsistent with major clinical practice guidelines; the available evidence suggested no beneficial effects of any therapies that researchers have evaluated in RCTs.

Fibromyalgia

In a randomized, controlled pilot study, Short et al (2011) examined the effects of adjunctive left pre-frontal rTMS on patients with fibromyalgia pain. A total of 20 patients with fibromyalgia, defined by American College of Rheumatology criteria, and were randomized to receive 4,000 pulses at 10 Hz TMS (n = 10), or sham TMS (n = 10) treatment for 10 sessions over 2 weeks along with their standard medications, which were fixed and stable for at least 4 weeks before starting sessions. Subjects recorded daily pain, mood, and activity. Blinded raters assessed pain, mood, functional status, and tender points weekly with the Brief Pain Inventory, Hamilton Depression Rating Scale, and Fibromyalgia Impact Questionnaire. No statistically significant differences between groups were observed. Patients who received active TMS had a mean 29 % (statistically significant) reduction in pain symptoms in comparison to their baseline pain. Sham-TMS participants had a 4 % non-significant change in daily pain from their baseline pain. At 2 weeks after treatment, there was a significant improvement in depression symptoms in the active group compared to baseline. Pain reduction preceded anti-depressant effects. TMS was well-tolerated, with few side effects. The authors concluded that further studies that address study limitations (small
sample size and short follow-up) are needed to determine whether daily prefrontal TMS may be an effective, durable, and clinically useful treatment for fibromyalgia symptoms.

Marlow et al (2013) systematically reviewed the literature to date applying rTMS or tDCS for patients with fibromyalgia syndrome (FMS). Electronic bibliography databases screened included PubMed, Ovid MEDLINE, PsychINFO, CINAHL, and Cochrane Library. The keyword "fibromyalgia" was combined with ("transcranial" and "stimulation") or "TMS" or "tDCS" or "transcranial magnetic stimulation" or "transcranial direct current stimulation". Nine of 23 studies were included; brain stimulation sites comprised either the primary motor cortex (M1) or the dorso-lateral pre-frontal cortex (DLPFC). Five studies used rTMS (high-frequency-M1: 2, low-frequency-DLPFC: 2, high-frequency-DLPFC: 1), while 4 applied tDCS (anodal-M1: 1, anodal-M1/DLPFC: 3); 8 were double-blinded RCTS. Most (80 %) rTMS studies that measured pain reported significant decreases, while all (100 %) tDCS studies with pain measures reported significant decreases. Greater longevity of significant pain reductions was observed for excitatory M1 rTMS/tDCS. The authors concluded that studies involving excitatory rTMS/tDCS at M1 showed analogous pain reductions as well as considerably fewer side effects compared to FDA-approved FMS pharmaceuticals. The most commonly reported side effects were mild, including transient headaches and scalp discomforts at the stimulation site. Yearly use of rTMS/tDCS regimens appears costly ($11,740 to 14,507/year); however, analyses to appropriately weigh these costs against clinical and quality of life benefits for patients with FMS are lacking. Consequently, rTMS/tDCS should be considered when treating patients with FMS, particularly those who are unable to find adequate symptom relief with other therapies. Moreover, they stated that further work into optimal stimulation parameters and standardized outcome measures is needed to clarify associated efficacy and effectiveness.

In a double-blind, randomized, placebo-controlled study, Boyer and colleagues (2014) examined the impact of rTMS on quality of life (QoL) of patients with fibromyalgia, and its possible brain metabolic substrate. A total of 38 patients were randomly assigned to receive high-frequency rTMS (n = 19) or sham stimulation (n = 19), applied to left primary motor cortex in 14 sessions over 10 weeks. Primary clinical outcomes were QoL changes at the end of week 11, measured using the Fibromyalgia Impact Questionnaire (FIQ). Secondary clinical outcomes were mental and physical QoL component measured using the 36-Item Short Form Health Survey (SF-36), but also pain, mood, and anxiety. Resting-state [(18)F]
-fluorodeoxyglucose-PET metabolism was assessed at baseline, week 2, and week 11. Whole-brain voxel-based analysis was performed to study between-group metabolic changes over time. At week 11, patients of the active rTMS group had greater QoL improvement in the FIQ (p = 0.032) and in the mental component of the SF-36 (p = 0.019) than the sham stimulation group. No significant impact was found for other clinical outcomes. Compared with the sham stimulation group, patients of the active rTMS group presented an increase in right medial temporal metabolism between baseline and week 11 (p < 0.001), which was correlated with FIQ and mental component SF-36 concomitant changes (r = -0.38, p = 0.043; r = 0.51, p = 0.009, respectively). Improvement of QoL involved mainly affective, emotional, and social dimensions. The authors concluded that the findings of this study showed that rTMS improves QoL of patients with fibromyalgia. This improvement is associated with a concomitant increase in right limbic metabolism, arguing for a neural substrate to the impact of rTMS on emotional dimensions involved in QoL. The major drawback of this study was its small sample size (n = 38). Furthermore, 9 patients did not complete the maintenance phase, reducing the sample size to 29. The authors stated that replication with a larger sample size is needed. They also noted that recent studies recommended that investigators test for the success of blinding, which was not done in this trial.

Winkelmann et al (2012) stated that the scheduled update to the German S3 guidelines on fibromyalgia syndrome by the Association of the Scientific Medical Societies was planned starting in March 2011. The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy, 9 scientific medical societies, as well as 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, PsycInfo, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Center for Evidence-Based Medicine. The formulation and grading of recommendations was accomplished using a multi-step, formal consensus process. The guidelines were reviewed by the boards of the participating scientific medical societies. The authors concluded that low-to-moderate intensity aerobic exercise and strength training are strongly recommended; chiropractic, laser therapy, magnetic field therapy, massage, and transcranial current stimulation are not recommended.
Saltychev and Laimi (2017) examined if there is evidence of rTMS being effective in decreasing the severity of pain among patients with fibromyalgia. CENTRAL, Medline, Embase, CINAHL, SCOPUS, Web Of Science, and relevant references of the identified studies were searched. Randomized controlled studies on adults with fibromyalgia were included. The outcome studied was change in pain severity. Methodological quality was assessed using the scale introduced in the Guidelines for Systematic Reviews in the Cochrane Collaboration Back Review Group. A random-effects meta-analysis was carried out with a test for heterogeneity using the I² and pooled estimate as a non-standardized mean of difference in change in pain severity measures by a numeric rating scale. The search resulted in 791 records, 8 relevant, and meta-analyses on 7 trials. The risk of bias was considered low for 7 studies. Pain severity before and after the last stimulation decreased by -1.2 points on 0 to 10 numeric rating scale (95 % CI: -1.7 to -0.8). Pain severity before and 1 week to 1 month after the last stimulation decreased by -0.7 points (95 % CI: -1.0 to -0.3). Both pooled results were below the minimal clinically important difference of 1.5 points. The authors concluded that there is moderate evidence that rTMS is not more effective than sham in reducing the severity of pain in fibromyalgia patients, questioning the routine recommendation of this method for fibromyalgia treatment.

Migraine

Funak and colleagues (2006) noted that in healthy volunteers (HV), 1 session of 1-Hz rTMS over the visual cortex induces dishabituation of visual evoked potentials (VEPs) on average for 30 mins, while in migraineurs 1 session of 10-Hz rTMS replaces the abnormal VEP potentiation by a normal habituation for 9 mins. These investigators examined if repeated rTMS sessions (1-Hz in 8 HV; 10-Hz in 8 migraineurs) on 5 consecutive days can modify VEPs for longer periods. In all 8 HV, the 1-Hz rTMS-induced dishabituation increased in duration over consecutive sessions and persisted between several hours (n = 4) and several weeks (n = 4) after the 5th session. In 6 of the 8 migraineurs, the normalization of VEP habituation by 10-Hz rTMS lasted longer after each daily stimulation, but did not exceed several hours after the last session, except in 2 patients, where it persisted for 2 days and 1 week. The authors concluded that daily rTMS can thus induce long-lasting changes in cortical excitability and VEP habituation pattern. However, whether this effect may be useful in preventing migraines remains to be determined.
Guidance from the National Institute for Health and Care Excellence (NICE, 2014) concluded that the evidence on the efficacy of TMS for the treatment of migraine is limited in quantity and for the prevention of migraine is limited in both quality and quantity. Evidence on its safety in the short and medium term is adequate but there is uncertainty about the safety of long-term or frequent use of TMS.

**Parkinson Disease**

Wagle-Shukla et al (2007) examined the effectiveness of rTMS for the treatment of patients (n = 6) with levodopa-induced dyskinesias (LID). They reported that a 2-week course of low-frequency rTMS reduced LID as indexed by both objective as well as subjective evaluations, with no change in parkinsonism as evaluated by Unified Parkinson Disease Rating Scale motor scores. The benefit was observed at 1 day after treatment, but not 2 weeks later. The drawbacks of this study were its small sample size and the open labeled design. Furthermore, benefits were not sustained. More research is needed to ascertain the clinical value, if any, of rTMS in the treatment of LID.

An assessment of rTMS by the Health Council of the Netherlands (2008) stated that the use of rTMS to treat patients with Parkinson’s disease has produced some encouraging results, and that this technology could be useful in identifying the best site for deep brain stimulation. The assessment stated that it is “still open to question” whether or not rTMS has the potential to reduce tremors.

In a randomized, double-blind, sham-controlled study, Benninger and colleagues (2011) examined the safety and effectiveness of intermittent theta-burst stimulation (iTBS) in the treatment of motor symptoms in Parkinson disease (PD); iTBS of the motor and DLPFC was investigated in 8 sessions over 2 weeks. Assessment of safety and clinical efficacy over a 1-month period included timed tests of gait and bradykinesia, Unified Parkinson's Disease Rating Scale (UPDRS), and additional clinical, neuropsychological, and neurophysiologic measures. These researchers investigated 26 patients with mild-to-moderate PD: 13 received iTBS and 13 sham stimulation. They found beneficial effects of iTBS on mood, but no improvement of gait, bradykinesia, UPDRS, and other measures. Electroencephalography/electromyography monitoring recorded no pathologic increase of cortical excitability or epileptic activity. Few reported discomfort or pain.

http://www.aetna.com/cpb/medical/data/400_499/0469.html 03/28/2019
and 1 subject experienced tinnitus during real stimulation. The authors concluded that iTBS of the motor and pre-frontal cortices appears safe and improves mood, but failed to improve motor performance and functional status in PD.

There are 2 non-invasive methods to stimulate the brain: (i) TMS, and (ii) tDCS. Compared to the former approach, the latter does not directly lead to neuronal discharges; tDCS only modulates the excitability level of brain tissue. Furthermore, tDCS can be employed in a dual mode -- increasing excitability on one hemisphere and decreasing excitability on the other hemisphere. In a randomized, double-blind, sham-controlled study, Benninger and colleagues (2010) examined the effectiveness of tDCS in the treatment of PD. The effectiveness of anodal tDCS applied to the motor and pre-frontal cortices was investigated in 8 sessions over 2.5 weeks. Assessment over a 3-month period included timed tests of gait (primary outcome measure) and bradykinesia in the upper extremities, UPDRS, Serial Reaction Time Task, Beck Depression Inventory, Health Survey and self-assessment of mobility. A total of 25 PD patients were investigated, 13 receiving tDCS and 12 sham stimulation. Transcranial direct current stimulation improved gait by some measures for a short time and improved bradykinesia in both the on and off states for longer than 3 months. Changes in UPDRS, reaction time, physical and mental well being, and self-assessed mobility did not differ between the tDCS and sham interventions. The authors concluded that tDCS of the motor and pre-frontal cortices may have therapeutic potential in PD, but better stimulation parameters need to be established to make the technique clinically viable.

In a randomized, double-blind, sham-controlled, multi-center study with a parallel design, Shirota et al (2013) examined the effectiveness and stimulation frequency dependence of rTMS over the supplementary motor area (SMA) in PD. A weekly intervention was performed 8 times, and the effects were monitored up to 20 weeks. By central registration, participants were assigned to 1 of 3 arms of the study: low-frequency (1-Hz) rTMS, high-frequency (10-Hz) rTMS, and realistic sham stimulation. The primary end point was the score change of the UPDRS part III from the baseline. Several non-motor symptom scales such as the Hamilton Rating Scale for Depression, apathy score, and non-motor symptoms questionnaire were defined as secondary end points. Of the 106 patients enrolled, 36 were allocated to 1-Hz rTMS, 34 to 10-Hz rTMS, and 36 to realistic sham stimulation. Results showed 6.84-point improvement of the UPDRS part III in the 1-Hz group at the last visit of the 20th week. Sham stimulation and 10-Hz rTMS improved motor symptoms transiently, but their effects disappeared in the observation period.
Changes in non-motor symptoms (NMS) were not clear in any group. No severe adverse event was reported. The authors concluded that 1-Hz rTMS over the SMA was effective for motor, but not non-motor, symptoms in PD. Moreover, they stated that rTMS is a promising add-on therapy for motor symptoms of PD, whereas establishment of an adequate protocol for NMS treatment using rTMS requires further study. They noted that the present findings warrant a confirmatory clinical trial for SMA rTMS on PD, undertaken on a larger scale.

In a systematic review, Chung and Mak (2016) evaluated the effectiveness of rTMS on improving physical function and motor signs over the short- and long-terms in people with PD. A total of 5 electronic databases were systematically searched for English language full-text articles using relevant search terms. Only randomized placebo-controlled trials investigating the effects of rTMS in PD were considered. The primary outcomes were walking performance, upper limb function, and UPDRS section III. Trials with similar outcomes were pooled by calculating Hedges’ g using random-effects model. A total of 22 trials comprising 555 people with PD were included. Pooled estimates of effect of rTMS indicated significantly improved short-term upper limb function (Hedges’ g, 0.40, p = 0.007), short-term (Hedges’ g, 0.61, p = 0.03) and long-term walking performance (Hedges’ g, 0.89, p = 0.03), short-term (Hedges’ g, 0.31, p = 0.003) and long-term (Hedges’ g, 0.54, p = 0.003) UPDRS III scores. Subgroup analyses suggested a more prominent effect for M1 stimulation. Meta-regression revealed that a greater number of total stimulation pulses were associated with more UPDRS III improvements over the long-term. The authors concluded that the pooled evidence suggested that rTMS improves upper limb function in the short-term, walking performance and UPDRS III in the short- and long-terms in PD sufferers. Moreover, they stated that further studies are needed to develop optimal rTMS therapeutic protocols for PD.

**Tinnitus**

In a pilot study, Smith et al (2007) evaluated the effectiveness of rTMS and its effects on attentional deficits and cortical asymmetry in 4 patients with chronic tinnitus using objective and subjective measures and employing an optimization technique refined in our laboratory. Patients received 5 consecutive days of active, low-frequency rTMS or sham treatment (using a 45-degree coil-tilt method) before crossing over. Subjective tinnitus was assessed at baseline, after each treatment, and 4 weeks later. Positron emission tomography/computed tomography (PET/CT) scans were obtained at baseline and immediately after active treatment to examine
change in cortical asymmetry. Attentional vigilance was assessed at baseline and after each treatment using a simple reaction time test. All patients had a response to active (but not sham) rTMS, as indicated by their best tinnitus ratings; however, tinnitus returned in all patients by 4 weeks after active treatment. All patients had reduced cortical activity visualized on PET immediately after active rTMS. Mean reaction time improved (p < 0.05) after active but not sham rTMS. The authors concluded that rTMS is a promising treatment modality that can transiently diminish tinnitus in some individuals, but further trials are needed to determine the optimal techniques required to achieve a lasting response. This is in agreement with the findings of Plewnia et al (2007) who reported that the effects of rTMS for patients with chronic tinnitus are only moderate; inter-individual responsiveness varied; and the attenuation of tinnitus appeared to wear off within 2 weeks after the last stimulation session.

In a pilot study, Lee and colleagues (2008) examined if rTMS may suppress excessive spontaneous activity in the left superior temporal gyrus associated with tinnitus. A total of 8 patients with tinnitus received 5 consecutive days of rTMS (0.5 Hz, 20 mins) to the left temporo-parietal area. Tinnitus Handicap Inventory (THI) measures before sessions 1 and 3 and after session 5 were used to evaluate effectiveness. Patient 1's THI decreased 40 to 34 to 26, patient 4 reported a subjective improvement, patient 8 withdrew, and the remaining patients reported no improvement. Adverse effects included temporary soreness, restlessness, and photophobia. The authors concluded that the parameters for this rTMS study are different from those that reported success with its use. With these current parameters, rTMS did not improve tinnitus. There were no permanent adverse outcomes.

Kleinjung et al (2009) investigated if administration of the dopamine precursor levodopa before low-frequency rTMS enhances its effectiveness in tinnitus treatment. A total of 16 patients with chronic tinnitus received 100 mg of levodopa before each session of low-frequency rTMS. Results were compared with a matched control group of 16 patients who received the same treatment, but without levodopa. Treatment outcome was assessed with a standardized tinnitus questionnaire. Both stimulation protocols resulted in a significant reduction of tinnitus scores after 10 days of stimulation; however, there was no significant difference between the 2 groups. The authors concluded that these findings suggested that 100 mg of levodopa does not enhance the effect of rTMS in the treatment of tinnitus. Furthermore, they stated that "[e]ven if the available data
clearly demonstrate the therapeutic potential of rTMS in tinnitus, the clinical effects are still relatively limited. A better understanding of the underlying neurobiological mechanisms will be crucial for optimizing stimulation protocols and further improving the efficacy of rTMS.

In a Cochrane review on rTMS for tinnitus, Meng et al (2011) concluded that there is very limited support for the use of low-frequency rTMS for the treatment of patients with tinnitus. When considering the impact of tinnitus on patients' quality of life, support is from a single study with a low-risk of bias based on a single outcome measure at a single point in time. When considering the impact on tinnitus loudness, this is based on the analysis of pooled data with a large confidence interval. Studies suggest that rTMS is a safe treatment for tinnitus in the short-term, however there were insufficient data to provide any support for the safety of this treatment in the long-term. The authors stated that more prospective, randomized, placebo-controlled, double-blind studies with large sample sizes are needed to confirm the effectiveness of rTMS for tinnitus patients. Uniform, validated, tinnitus-specific questionnaires and measurement scales should be used in future studies.

In a systematic review, Peng et al (2012) evaluated the effectiveness of rTMS for the treatment of chronic tinnitus. Data Sources Relevant electronic databases and a reference list of articles published up to January 2012 were searched. Randomized controlled clinical trials of all types of rTMS treatment for patients with chronic tinnitus were included. A total of 5 trials (160 participants) were included in this review. Repetitive TMS showed benefits in the short-term, but the long-term effects are questionable. The Tinnitus Handicap Inventory (THI) and the visual analog scale (VAS) were the major assessment methods used. After active TMS stimulation, the reduction in the THI total score and VAS was significant compared with baseline at the first time-point assessed and in the short-term (2 weeks and 4 weeks). The longest follow-up time was 26 weeks after treatment, and the shortest follow-up time was 2 weeks. No severe side effects were reported from the use of rTMS. Differences in age, hearing level, duration of tinnitus of the included patients, and the condition of sham treatment may influence the effect. The authors concluded that rTMS could be a new therapeutic tool for the treatment of chronic tinnitus, and thus far they have not been able to demonstrate any substantial risk from rTMS treatment. However, they stated that the long-term effects of rTMS treatment for tinnitus are not clear and will require further study.
Plewnia et al (2012) examined if 4 weeks of bilateral rTMS to the temporal or temporo-parietal cortex is effective and safe in the treatment of chronic tinnitus. In this controlled 3-armed trial, 48 patients with chronic tinnitus were treated with 4 weeks (20 sessions) of bilateral continuous theta burst stimulation (cTBS). They were randomized to stimulation above the temporal cortex, the temporo-parietal cortex, or as sham condition behind the mastoid. Patients were masked for the stimulation condition. Tinnitus severity was assessed after 2 and primarily 4 weeks of treatment and at 3 months follow-up with the tinnitus questionnaire and by a tinnitus change score. Audiologic safety was monitored by pure-tone and speech audiometry after 2 and 4 weeks of cTBS. Tinnitus severity was slightly reduced from baseline by a mean (SD) 2.6 (8.2) after sham, 2.4 (8.0) after temporo-parietal, 2.2 (8.3) after temporal treatment of 16 patients each, but there was no significant difference between sham treatments and temporal (CI: -5.4 to +6.7) or temporo-parietal cTBS (CI: -5.9 to +6.3) or real cTBS (CI: -7 to +5.1). Patients' global evaluation of tinnitus change after treatment did not indicate any effects. Audiologic measures were unaffected by treatment. The authors concluded that treating chronic tinnitus for 4 weeks by applying cTBS to the temporal or temporo-parietal cortex of both hemispheres appears to be safe but not more effective than sham stimulation. However, these results are not to be generalized to all forms of rTMS treatments for tinnitus.

In an editorial that accompanied the afore-mentioned study, Triggs and Hajioff (2012) stated that “At present, rTMS should be classified as “U” by the American Academy of Neurology classification of recommendation: the data are inadequate and conflicting, and the treatment is unproven”.

The American Academy of Otolaryngology - Head and Neck Surgery’s clinical practice guideline on “Tinnitus” (Tunkel et al, 2014) listed transcranial magnetic stimulation as one of the interventions were considered but no recommendation was made or were recommended against.

Anxiety Disorders

Prasko et al (2007) examined if rTMS would facilitate effect of serotonin reuptake inhibitors (SRIs) in patients with panic disorder (n = 15). Patients suffering from panic disorder resistant to SRI therapy were randomly assigned to either active or to sham rTMS. The objective of the study was to compare the 2- and 4-weeks effectiveness of the 10 sessions low-frequency rTMS with sham rTMS add on SRI
therapy. These researchers used 1-Hz, 30-min rTMS, 110 % of motor threshold administered over the right dorso-lateral prefrontal cortex (DLPFC). The same time schedule was used for sham administration. Psychopathology was evaluated by means of the rating scales CGI, HAMA, PDSS and BAI before the treatment, immediately after the experimental treatment, and 2 weeks after the experimental treatment by an independent reviewer. Both groups improved during the study period but the treatment effect did not differ between groups in any of the instruments. The authors concluded that low-frequency rTMS administered over the right dorso-lateral prefrontal cortex after 10 sessions did not differ from sham rTMS add on SRIs in patients with panic disorder.

Pigot and colleagues (2008) noted that rTMS has also been investigated for the treatment of some anxiety disorders (e.g., obsessive-compulsive disorder, post-traumatic stress disorder and panic disorder). While anecdotal reports and open studies have suggested a therapeutic role for rTMS in anxiety disorders, controlled studies, which have varied greatly in terms of rTMS administration, have not shown it to be superior to placebo. Furthermore, reports in animal models of anxiety have not been consistent. Thus, there is currently no convincing evidence for the clinical role of rTMS in the treatment of anxiety disorders. The authors stated that more research is needed, drawing on advances in the understanding of pathological neurocircuitry in anxiety disorders and the mechanisms of action by which rTMS may alter that neurocircuitry. In a review on OCD, Abramowitz and colleagues (2009) stated that although rTMS has not been extensively assessed in this disorder, available data do not support its therapeutic efficacy for this condition.

Berlim et al (2014) stated that rTMS applied to the dorsolateral prefrontal cortex (DLPFC) has yielded promising results as a treatment for post-traumatic stress disorder (PTSD). However, to-date, no quantitative review of its clinical utility has been published. These investigators searched for randomized and sham-controlled trials from 1995 to March 2013 using MEDLINE, Embase, PsycINFO, CENTRAL, and SCOPUS. They then performed an exploratory random effects meta-analysis. Studies on rTMS applied to the right DLPFC included 64 adults with PTSD. The pooled Hedges g effect size for pre- and post-changes in clinician-rated and self-reported PTSD symptoms were, respectively, 1.65 (p < 0.001) and 1.91 (p < 0.001), indicating significant and large-sized differences in outcome favoring active rTMS. Also, there were significant pre- and post-decreases with active rTMS in overall anxiety (Hedges g = 1.24; p = 0.02) and depressive (Hedges g = 0.85; p < 0.001) symptoms. Drop-out rates at study end did not differ between active and sham
rTMS groups. Regarding rTMS applied to the left DLPFC, there was only 1 study published to-date (using a high frequency protocol), and its results showed that active rTMS seems to be superior overall to sham rTMS. The authors concluded that this exploratory meta-analysis showed that active rTMS applied to the DLPFC seems to be effective and acceptable for treating PTSD. However, they stated that the small number of subjects included in the analyses limits the generalizability of these findings. They stated that future studies should include larger samples and deliver optimized stimulation parameters.

An assessment by the Canadian Agency for Drugs and Technologies in Health (CADTH, 2014) concluded that, for PTSD, there is early evidence that TMS may improve clinical outcomes. For generalized anxiety disorder, no evidence was found.

Spasticity

Centonze and associates (2007) examined if investigate rTMS can modify spasticity. These researchers used high-frequency (5 Hz) and low-frequency (1 Hz) rTMS protocols in 19 remitting patients with relapsing-remitting multiple sclerosis and lower limb spasticity. A single session of 1 Hz rTMS over the leg primary motor cortex increased H/M amplitude ratio of the soleus H reflex, a reliable neurophysiologic measure of stretch reflex. Five hertz rTMS decreased H/M amplitude ratio of the soleus H reflex and increased cortico-spinal excitability. Single sessions did not induce any effect on spasticity. A significant improvement of lower limb spasticity was observed when rTMS applications were repeated during a 2-week period. Clinical improvement was long-lasting (at least 7 days after the end of treatment) when patients underwent 5 Hz rTMS treatment during a 2-week protocol. No effect was obtained after a 2-week sham stimulation. The authors concluded that rTMS may improve spasticity in multiple sclerosis. The findings of this study need to be validated by prospective RCTs with larger patient numbers.

Bulemia Nervosa

In a single-center, randomized, double-blind, sham-controlled study, Walpoth et al (2008) examined the effects of rTMS in bulimia nervosa (BN). A total of 14 women meeting DSM-IV criteria for BN were included in the study. In order to exclude patients highly responsive to placebo, all patients were first submitted to a 1-week
sham treatment. Randomization was followed by 3 weeks of active treatment or sham stimulation. The main outcome was the change in binges and purges. Secondary outcome variables were the decrease of the Hamilton Depression Rating Scale (HDRS), the Beck Depression Inventory (BDI) and the Yale-Brown Obsessive Compulsive Scale (YBOCS) over time. The average number of binges per day declined significantly between baseline and the end of treatment in the 2 groups. There was no significant difference between sham and active stimulation in terms of purge behavior, BDI, HDRS and YBOCS over time. The authors concluded that these preliminary results indicated that rTMS in the treatment of BN does not exert additional benefit over placebo.

Schizophrenia

Freitas and colleagues (2009) performed meta-analyses of all prospective studies of the therapeutic application of rTMS in refractory schizophrenia assessing the effects of high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) to treat negative symptoms, and low-frequency rTMS to the left temporo-parietal cortex (TPC) to treat auditory hallucinations (AH) and overall positive symptoms. When analyzing controlled (active arms) and uncontrolled studies together, the effect sizes showed significant and moderate effects of rTMS on negative and positive symptoms (based on PANSS-N or SANS, and PANSS-P or SAPS, respectively). However, the analysis for the sham-controlled studies revealed a small non-significant effect size for negative (0.27, p = 0.417) and for positive symptoms (0.17, p = 0.129). When specifically analyzing AH (based on AHRS, HCS or SAH), the effect size for the sham-controlled studies was large and significant (1.04; p = 0.002). The authors concluded that these meta-analyses support the need for further controlled, larger trials to assess the clinical efficacy of rTMS on negative and positive symptoms of schizophrenia, while suggesting the need for exploration for alternative stimulation protocols.

An assessment by the Health Council of the Netherlands (2008) stated that studies of rTMS for hallucinations in schizophrenic patients are both fewer in number and more restricted in scope than in the case of depression.

Slotema et al (2012) provided an update of the literature on the efficacy of rTMS for auditory verbal hallucinations (AVH) and investigated the effect of rTMS 1 month after the end of treatment. A literature search was performed from 1966 through August 2012 using Cochrane Central Register of Controlled Trials, Cochrane
Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Embase Psychiatry, Ovid Medline, PsycINFO and PubMed. Randomized, double-blind, sham-controlled studies with severity of AVH or severity of psychosis as an outcome measure were included. Data were obtained from 17 randomized studies of rTMS for AVH; 5 studies fulfilled the criteria for the meta-analysis on the effect of rTMS 1 month after the end of treatment. Standardized mean weighted effect sizes of rTMS versus sham were computed on pre- and post-treatment comparisons. The mean weighted effect size of rTMS directed at the left temporo-parietal area was 0.44 (95 % CI: 0.19 to 0.68). A separate meta-analysis including studies directing rTMS at other brain regions revealed a mean weighted effect size of 0.33 (95 % CI: 0.17 to 0.50) in favor of real TMS. The effect of rTMS was no longer significant at 1 month of follow-up (mean weighted effect size = 0.40, 95 % CI: -0.23 to 0.102). Side effects were mild and the number of dropouts in the real TMS group was not significantly higher than in the sham group. The authors concluded that with the inclusion of studies with larger patient samples, the mean weighted effect size of rTMS directed at the left temporo-parietal area for AVH has decreased, although the effect is still significant. The duration of the effect of rTMS may be less than 1 month. Moreover, they stated that more research is needed in order to optimize parameters and further evaluate the clinical relevance of this intervention.

Stroke

Khedr et al (2009a) examined the therapeutic effect of rTMS on post-stroke dysphagia. A total of 26 patients with post-stroke dysphagia due to mono-hemispheric stroke were randomly allocated to receive real (n = 14) or sham (n = 12) rTMS of the affected motor cortex. Each patient received a total of 300 rTMS pulses at an intensity of 120 % hand motor threshold for 5 consecutive days. Clinical ratings of dysphagia and motor disability were assessed before and immediately after the last session and then again after 1 and 2 months. The amplitude of the motor-evoked potential (MEP) evoked by single-pulse TMS was also assessed before and at 1 month in 16 of the patients. There were no significant differences between patients who received real rTMS and the sham group in age, hand grip strength, Barthel Index or degree of dysphagia at the baseline assessment. Real rTMS led to a significantly greater improvement compared with sham in dysphagia and motor disability that was maintained over 2 months of follow-up. This was accompanied by a significant increase in the amplitude of the esophageal MEP evoked from either the stroke or non-stroke
hemisphere. The authors concluded that rTMS may be a useful adjunct to conventional therapy for dysphagia after stroke. These findings need to be validated by well-designed studies.

Regarding the use of rTMS in stroke, the Health Council of the Netherlands (2008) found that few articles have been published on this topic, and that this limited amount of published data reveals only short-term, marginal improvements.

Avenanti et al (2012) examined the long-term behavioral and neurophysiologic effects of combined time-locked rTMS and physical therapy (PT) intervention in chronic stroke patients with mild motor disabilities. A total of 30 patients were enrolled in a double-blind, randomized, single-center clinical trial. Patients received 10 daily sessions of 1 Hz rTMS over the intact motor cortex. In different groups, stimulation was either real (rTMS(R)) or sham (rTMS(S)) and was administered either immediately before or after PT. Outcome measures included dexterity, force, inter-hemispheric inhibition, and corticospinal excitability and were assessed for 3 months after the end of treatment. Treatment induced cumulative rebalance of excitability in the 2 hemispheres and a reduction of inter-hemispheric inhibition in the rTMS(R) groups. Use-dependent improvements were detected in all groups. Improvements in trained abilities were small and transitory in rTMS(S) patients. Greater behavioral and neurophysiologic outcomes were found after rTMS(R), with the group receiving rTMS(R) before PT (rTMS(R)-PT) showing robust and stable improvements and the other group (PT-rTMS(R)) showing a slight improvement decline over time. The authors concluded that these findings indicated that priming PT with inhibitory rTMS is optimal to boost use-dependent plasticity and rebalance motor excitability and suggest that time-locked rTMS is a valid and promising approach for chronic stroke patients with mild motor impairment. Furthermore, the authors stated that "[f]urther studies are needed to evaluate the effect of intervention order of time-locked rTMS in the same patients. Moreover, future studies should assess whether the present findings can be extended to stroke patients with moderate to severe motor impairments".

Corti et al (2012) stated that conceptually rTMS could be used therapeutically to restore the balance of inter-hemispheric inhibition after stroke. Repetitive TMS has been used in 2 ways: (i) low-frequency stimulation (less than or equal to 1 Hz) to the motor cortex of the unaffected hemisphere to reduce the excitability of the contralesional hemisphere or (ii) high-frequency stimulation (greater than 1 Hz) to the motor cortex of the affected hemisphere (AH) to increase excitability of the
ipsilesional hemisphere. These investigators reviewed evidence regarding the safety and effectiveness of high-frequency rTMS to the motor cortex of the AH. The studies included investigated the concurrent effects of rTMS on the excitability of corticospinal pathways and upper-limb motor function in adults after stroke. The findings of this review suggested that rTMS applied to the AH is a safe technique and could be considered an effective approach for modulating brain function and contributing to motor recovery after stroke. The authors concluded that although the studies included in this review provided important information, double-blinded, sham-controlled phase II and phase III clinical trials with larger sample sizes are needed to validate this novel therapeutic approach.

In a comparative case study, Plow et al (2011) attempted to standardize a protocol for promoting visual rehabilitative outcomes in post-stroke hemianopia by combining occipital cortical tDCS with vision restoration therapy (VRT). Two patients, both with right hemianopia after occipital stroke damage were included in this study. Both patients underwent an identical VRT protocol that lasted 3 months (30 mins, twice-daily, 3 days/week). In patient 1, anodal tDCS was delivered to the occipital cortex during VRT training, whereas in patient 2 sham tDCS with VRT was performed. The primary outcome, visual field border, was defined objectively by using high-resolution perimetry. Secondary outcomes included subjective characterization of visual deficit and functional surveys that assessed performance on activities of daily living. For patient 1, the neural correlates of visual recovery were also investigated, by using functional magnetic resonance imaging. Delivery of combined tDCS with VRT was feasible and safe. High-resolution perimetry revealed a greater shift in visual field border for patient 1 versus patient 2. Patient 1 also showed greater recovery of function in activities of daily living. Contrary to the expectation, patient 2 perceived greater subjective improvement in visual field despite objective high-resolution perimetry results that indicated otherwise. In patient 1, visual function recovery was associated with functional magnetic resonance imaging activity in surviving peri-lesional and bilateral higher-order visual areas. The authors concluded that these findings of preliminary case comparisons suggested that occipital cortical tDCS may enhance recovery of visual function associated with concurrent VRT through visual cortical re-organization. They stated that future studies may benefit from incorporating protocol refinements such as those described here, which include global capture of function, control for potential confounds, and investigation of underlying neural substrates of recovery.
Szafliarsk et al (2011) stated that aphasia affects 1/3 of stroke patients with improvements noted only in some of them. The goal of this exploratory study was to provide preliminary evidence regarding safety and effectiveness of functional magnetic resonance imaging (fMRI)-guided excitatory rTMS applied to the residual left-hemispheric Broca's area for chronic aphasia treatment. These researchers enrolled 8 patients with moderate or severe aphasia of more than 1 year after left middle cerebral artery stroke. Linguistic battery was administered pre-/post-rTMS; a semantic decision/tone decision (SDTD) fMRI task was used to localize left-hemispheric Broca's area. Repetitive TMS protocol consisted of 10 daily treatments of 200 seconds each using an excitatory stimulation protocol called intermittent theta burst stimulation (iTBS). Coil placement was targeted individually to the left Broca’s. A total of 6 patients showed significant pre-/post-rTMS improvements in semantic fluency (p = 0.028); they were able to generate more appropriate words when prompted with a semantic category. Pre-/post-rTMS fMRI maps showed increases in left fronto-temporo-parietal language networks with a significant left-hemispheric shift in the left frontal (p = 0.025), left temporo-parietal (p = 0.038) regions and global language LI (p = 0.018). Patients tended to report subjective improvement on Communicative Activities Log (mini-CAL; p = 0.075). None of the subjects reported ill effects of rTMS. The authors concluded that fMRI-guided, excitatory rTMS applied to the affected Broca's area improved language skills in patients with chronic post-stroke aphasia; these improvements correlated with increased language lateralization to the left hemisphere. They stated that this rTMS protocol appears to be safe and should be further tested in blinded studies assessing its short- and long-term safety/effectiveness for post-stroke aphasia rehabilitation.

Kakuda et al (2012a) stated that both low-frequency rTMS (LF-rTMS) and intensive occupational therapy (OT) have been recently reported to be clinically beneficial for post-stroke patients with upper limb hemiparesis. Based on these reports, these researchers developed an inpatient combination protocol of these 2 modalities for the treatment of such patients. In a pilot study, these investigators examined the safety and feasibility of the protocol in a large number of patients from different institutions, and identified predictors of the clinical response to the treatment. The study subjects were 204 post-stroke patients with upper limb hemiparesis (mean age at admission of 58.5 +/- 13.4 years, mean time after stroke of 5.0 +/- 4.5 years, +/- SD) from 5 institutions in Japan. During 15-day hospitalization, each patient received 22 treatment sessions of 20-min LF-rTMS and 120-min intensive OT daily. Low-frequency rTMS of 1 Hz was applied to the contralesional hemisphere.
over the primary motor area. The intensive OT, consisting of 60-min 1-on-1 training and 60-min self-exercise, was provided after the application of LF-rTMS. Fugl-Meyer Assessment (FMA) and Wolf Motor Function Test (WMFT) were performed serially. The physiatrists and occupational therapists involved in this study received training prior to the study to standardize the therapeutic protocol. All patients completed the protocol without any adverse effects. The FMA score increased and WMFT log performance time decreased significantly at discharge, relative to the respective values at admission (change in FMA score: median at admission, 47 points; median at discharge, 51 points; \( p < 0.001 \)). change in WMFT log performance time: median at admission, 3.23; median at discharge, 2.51; \( p < 0.001 \)). These changes were persistently seen up to 4 weeks after discharge in 79 patients. Linear regression analysis found no significant relationship between baseline parameters and indexes of improvement in motor function. The authors concluded that the 15-day inpatient rTMS plus OT protocol is a safe, feasible, and clinically useful neuro-rehabilitative intervention for post-stroke patients with upper limb hemiparesis. The response to the treatment was not influenced by age or time after stroke onset. They stated that the effectiveness of the intervention should be confirmed in a randomized controlled study including a control group.

Kakuda et al (2012b) noted that for spastic upper limb hemiparesis after stroke, they developed triple-element protocol of botulinum toxin type A (BoNTA) injection, LF-rTMS, and intensive OT. These researchers investigated the safety and feasibility of the protocol. A total of 14 post-stroke patients with spastic upper limb hemiparesis (mean age of 54.9 +/- 9.2 years, time after onset: 87.1 +/- 48.2 months, +/- SD) were included in this study. In all patients, BoNTA was injected into spastic muscles of the affected upper limb (maximum total dose: 240 units). Four weeks later, they were hospitalized to receive 22 sessions of 20-min LF-rTMS and 120-min intensive OT daily over 15 days. Motor function of the affected upper limb was evaluated mainly using FMA, WMFT, motor activity log (MAL), and the severity of spasticity was measured with modified Ashworth scale (MAS) at BoNTA injection, discharge and 4 weeks post-discharge. All patients completed the protocol without any adverse effects. The FMA score and MAL scores, but not WMFT performance time, improved significantly at discharge. The MAS score of all examined muscles decreased significantly between BoNTA and discharge. The beneficial effect of the protocol on motor function and spasticity was almost maintained until 4 weeks after discharge. The authors concluded that the protocol is safe and feasible, although further larger studies are needed to confirm its effectiveness.
Ayache et al (2012) stated that non-invasive cortical stimulation (NICS) has been used during the acute, post-acute and chronic post-stroke phases to improve motor recovery in stroke patients having upper- and/or lower-limb paresis. These investigators reviewed the rationale for using the different NICS modalities to promote motor stroke rehabilitation. A number of open and placebo-controlled trials have investigated the clinical effect of rTMS or tDCS of the primary motor cortex in patients with motor stroke. These studies attempted to improve motor performance by increasing cortical excitability in the stroke-affected hemisphere (via HF- rTMS or anodal tDCS) or by decreasing cortical excitability in the contralateral hemisphere (via LF- rTMS or cathodal tDCS). The goal of these studies was to reduce the inhibition exerted by the unaffected hemisphere on the affected hemisphere and to then restore a normal balance of inter-hemispheric inhibition. All these NICS techniques administered alone or in combination with various methods of neuro-rehabilitation were found to be safe and equally effective at the short-term on various aspects of post-stroke motor abilities. However, they stated that the long-term effect of NICS on motor stroke needs to be further evaluated before considering the use of such a technique in the daily routine management of stroke.

Corti et al (2012) stated that rTMS is known to modulate cortical excitability and has thus been suggested to be a therapeutic approach for improving the efficacy of rehabilitation for motor recovery after stroke. In addition to producing effects on cortical excitability, stroke may affect the balance of trans-callosal inhibitory pathways between motor primary areas in both hemispheres: the affected hemisphere (AH) may be disrupted not only by the infarct itself but also by the resulting asymmetric inhibition from the unaffected hemisphere, further reducing the excitability of the AH. Conceptually, therefore, rTMS could be used therapeutically to restore the balance of inter-hemispheric inhibition after stroke. Repetitive TMS has been used in 2 ways: LF stimulation (less than or equal to 1 Hz) to the motor cortex of the unaffected hemisphere to reduce the excitability of the contralesional hemisphere or HF stimulation (greater than 1 Hz) to the motor cortex of the AH to increase excitability of the ipsilesional hemisphere. These researchers collated evidence regarding the safety and efficacy of HF- rTMS to the motor cortex of the AH. The studies included investigated the concurrent effects of rTMS on the excitability of cortico-spinal pathways and upper-limb motor function in adults after stroke. The findings of this review suggested that rTMS applied to the AH is a safe technique and could be considered an effective approach for modulating brain function and contributing to motor recovery after stroke. The authors concluded
that although the studies included in this review provided important information, double-blinded, sham-controlled phase II and phase III clinical trials with larger sample sizes are needed to validate this novel therapeutic approach.

In an evidence-based review, Wong and Tsang (2013) reported an updated evaluation and critical appraisal of available studies that investigated the effectiveness of rTMS on post-stroke aphasia rehabilitation. A literature search was performed to identify studies that investigated the therapeutic effects of rTMS on post-stroke aphasia in various electronic databases, from their inception to 2011. The selected studies were classified according to the types of participants, types of interventions, outcome measures, and results. The methodological qualities of the selected studies were evaluated using the Physiotherapy Evidence Database scale. The current review was based on 12 studies, including open-label designs and controlled trials, which showed a positive effect of rTMS, with or without conventional rehabilitation, on post-stroke aphasia compared with sham or conventional rehabilitation alone. About 41% of the selected studies reported the long-term effect of rTMS on aphasia recovery. No adverse effect was reported. The authors concluded that the current review revealed that rTMS with or without conventional rehabilitation has positive effects on post-stroke aphasia. The studies also contributed to the plausible mechanisms of stroke recovery. However, they stated that with the concerns over the methodology of the selected studies in this review, a larger-scale, multi-center, well-designed RCT involving different phases and types of aphasia needs to be carried out before recommending rTMS as a complementary treatment for post-stroke aphasia.

In a meta-analysis, Hsu et al (2012) investigated the effects of rTMS on upper limb motor function in patients with stroke. These investigators searched for RCTs published between January 1990 and October 2011 in PubMed, Medline, Cochrane, and CINAHL using the following key words: stroke, cerebrovascular accident, and repetitive transcranial magnetic stimulation. The mean effect size and a 95% CI were estimated for the motor outcome and motor threshold using fixed and random effect models. Eighteen of the 34 candidate articles were included in this analysis. The selected studies involved a total of 392 patients. A significant effect size of 0.55 was found for motor outcome (95% CI: 0.37 to 0.72). Further sub-group analyses demonstrated more prominent effects for subcortical stroke (mean effect size, 0.73; 95% CI: 0.44 to 1.02) or studies applying low-frequency rTMS (mean effect size, 0.69; 95% CI: 0.42 to 0.95). Only 4 patients of the 18 articles included in this analysis reported adverse effects from rTMS. The
authors concluded that rTMS has a positive effect on motor recovery in patients with stroke, especially for those with subcortical stroke. Low-frequency rTMS over the unaffected hemisphere may be more beneficial than high-frequency rTMS over the affected hemisphere. Recent limited data suggested that intermittent theta-burst stimulation over the affected hemisphere might be a useful intervention. They stated that further well-designed studies in a larger population are needed to better elucidate the differential roles of various rTMS protocols in stroke treatment.

In a Cochrane review, Hao and colleagues (2013) evaluated the safety and effectiveness of rTMS for improving function in people with stroke. These investigators searched the Cochrane Stroke Group Trials Register (April 2012), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 4), the Chinese Stroke Trials Register (April 2012), MEDLINE (1950 to May 2012), EMBASE (1980 to May 2012), Science Citation Index (1981 to April 2012), Conference Proceedings Citation Index-Science (1990 to April 2012), CINAHL (1982 to May 2012), AMED (1985 to May 2012), PEDro (April 2012), REHABDATA (April 2012) and CIRRIE Database of International Rehabilitation Research (April 2012). In addition, they searched 5 Chinese databases, ongoing trials registers and relevant reference lists. These researchers included RCTs comparing rTMS therapy with sham therapy or no therapy. They excluded trials that reported only laboratory parameters. Two review authors independently selected trials, assessed trial quality and extracted the data. They resolved disagreements by discussion. A total of 19 trials involving a total of 588 participants were included in this review. Two heterogenous trials with a total of 183 subjects showed that rTMS treatment was not associated with a significant increase in the Barthel Index score (mean difference (MD) 15.92, 95 % CI: -2.11 to 33.95). Four trials with a total of 73 participants were not found to have a statistically significant effect on motor function (standardized mean difference (SMD) 0.51, 95 % CI: -0.99 to 2.01). Subgroup analyses of different stimulation frequencies or duration of illness also showed no significant difference. Few mild adverse events were observed in the rTMS groups, with the most common events being transient or mild headaches (2.4 %, 8/327) and local discomfort at the site of the stimulation. The authors concluded that current evidence does not support the routine use of rTMS for the treatment of stroke. Moreover, they stated that further trials with larger sample sizes are needed to determine a suitable rTMS protocol and the long-term functional outcome.
In a Cochrane review, Elsner et al (2013a) examined the effects for improving aphasia in patients after stroke. These investigators searched the Cochrane Stroke Group Trials Register (April 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, March 2012), MEDLINE (1948 to March 2012), EMBASE (1980 to March 2012), CINAHL (1982 to March 2012), AMED (1985 to April 2012), Science Citation Index (1899 to April 2012) and 7 additional databases. They also searched trials registers and reference lists, hand-searched conference proceedings and contacted authors and equipment manufacturers. These researchers included only RCTs and randomized controlled cross-over trials (from which they only analyzed the first period as a parallel group design) comparing tDCS versus control in adults with aphasia due to stroke. Two review authors independently assessed trial quality and extracted the data. If necessary, they contacted study authors for additional information. These investigators collected information on drop-outs and adverse events from the trials. They included 5 trials involving 54 participants. None of the included studies used any formal outcome measure for measuring functional communication, which is measuring aphasia in a real-life communicative setting. All 5 trials measured correct picture naming as a surrogate for aphasia. There was no evidence that tDCS enhanced speech and language therapy outcomes. No adverse events were reported and the proportion of drop-outs was comparable between groups. The authors concluded that currently there is no evidence of the effectiveness of tDCS (anodal tDCS, cathodal tDCS) versus control (sham tDCS). Moreover, they stated that it appears that cathodal tDCS over the non-lesioned hemisphere might be the most promising approach.

In a Cochrane review, Elsner et al (2013b) examined the effects of tDCS on generic activities of daily living (ADLs) and motor function in people with stroke. These investigators searched the Cochrane Stroke Group Trials Register (March 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, May 2013), MEDLINE (1948 to May 2013), EMBASE (1980 to May 2013), CINAHL (1982 to May 2013), AMED (1985 to May 2013), Science Citation Index (1899 to May 2013) and 4 additional databases. In an effort to identify further published, unpublished and ongoing trials, these investigators searched trials registers and reference lists, hand-searched conference proceedings and contacted authors and equipment manufacturers. They included only RCTs and randomized controlled cross-over trials (from which they analyzed only the first period as a parallel-group design) that compared tDCS versus control in adults with stroke for improving ADL performance and function. Two review authors independently
assessed trial quality and extracted data. If necessary, these researchers contacted study authors to ask for additional information. They collected information on drop-outs and adverse events from the trial reports. These researchers included 15 studies involving a total of 455 participants. Analysis of 6 studies involving 326 participants regarding the primary outcome, ADL, showed no evidence of an effect in favor of tDCS at the end of the intervention phase (mean difference (MD) 5.31 Barthel Index points; 95% CI: -0.52 to 11.14; inverse variance method with random-effects model), whereas at follow-up (MD 11.13 Barthel Index points; 95% CI: 2.89 to 19.37; inverse variance method with random-effects model), these investigators found evidence of an effect. However, the CIs were wide and the effect was not sustained when only studies with low-risk of bias were included. For the secondary outcome, upper limb function, these investigators analyzed 8 trials with 358 participants, which showed evidence of an effect in favor of tDCS at the end of the intervention phase (MD 3.45 Upper Extremity Fugl-Meyer Score points (UE-FM points); 95% CI: 1.24 to 5.67; inverse variance method with random-effects model) but not at the end of follow-up 3 months after the intervention (MD 9.23 UE-FM points; 95% CI: -13.47 to 31.94; inverse variance method with random-effects model). These results were sensitive to inclusion of studies at high-risk of bias. Adverse events were reported and the proportions of drop-outs and adverse events were comparable between groups (risk difference (RD) 0.00; 95% CI: -0.02 to 0.03; Mantel-Haenszel method with random-effects model). The authors concluded that evidence of very low to low quality is available on the effectiveness of tDCS (anodal/cathodal/dual) versus control (sham/any other intervention) for improving ADL performance and function after stroke. Moreover, they stated that future research should investigate the effects of tDCS on lower limb function and should address methodological issues by routinely reporting data on adverse events and drop-outs and allocation concealment, and by performing intention-to-treat analyses.

In a RCT with a 4-week follow-up, Barros Galvao et al (2014) examined the effectiveness of inhibitory rTMS for decreasing upper-limb muscle tone after chronic stroke. Patients with stroke (n = 20) with post-stroke upper limb spasticity were enrolled in this study. The experimental group received rTMS to the primary motor cortex of the unaffected side (1,500 pulses; 1Hz; 90% of resting motor threshold for the first dorsal interosseous muscle) in 10 sessions, 3 days/week, and physical therapy (PT). The control group received sham stimulation and PT. Main outcome measures were MAS, upper-extremity Fugl-Meyer assessment, FIM, range of motion, and stroke-specific quality-of-life scale. All outcomes were measured at
baseline, after treatment (post-intervention), and at a 4-week follow-up. A clinically important difference was defined as a reduction of greater than or equal to 1 in the MAS score. Friedman test revealed that PT is efficient for significantly reducing the upper limb spasticity of patients only when it is associated with rTMS. In the experimental group, 90% of the patients at post-intervention and 55.5% at follow-up showed a decrease of greater than or equal to 1 in the MAS score, representing clinically important differences. In the control group, 30% of the patients at post-intervention and 22.2% at follow-up experienced clinically meaningful changes. There were no differences between the groups at any time for any of the other outcome measures, indicating that both groups demonstrated similar behaviors over time for all variables. The authors concluded that rTMS associated with PT can be beneficial in reducing post-stroke spasticity. Moreover, they stated that more studies are needed to clarify the clinical changes underlying the reduction in spasticity induced by non-invasive brain stimulations.

In a randomized, controlled, double-blind clinical trial, Kirton and colleagues (2017) examined if the addition of tDCS to intensive therapy increases motor function in children with perinatal stroke and hemiparetic cerebral palsy (CP). Participants were recruited from a population-based cohort with MRI-classified unilateral perinatal stroke, aged 6 to 18 years, and disabling hemiparesis. All completed a goal-directed, peer-supported, 2-week after-school motor learning camp (32 hours of therapy). Participants were randomized 1:1 to 1 mA cathodal tDCS over the contralesional primary motor cortex (M1) for the initial 20 minutes of daily therapy or sham. Primary subjective (Canadian Occupational Performance Measure [COPM]), objective (Assisting Hand Assessment [AHA]), safety, and secondary outcomes were measured at 1 week and 2 months after intervention. Analysis was by intention-to-treat. A total of 24 participants were randomized (median age of 11.8 ± 2.7 years, range of 6.7 to 17.8); COPM performance and satisfaction scores doubled at 1 week with sustained gains at 2 months (p < 0.001); COPM scores increased more with tDCS compared to sham control (p = 0.004); AHA scores demonstrated only mild increases at both time points with no tDCS effects. Procedures were safe and well-tolerated with no decrease in either arm function or serious adverse events (AEs). The authors concluded that tDCS trials appeared feasible and safe in hemiparetic children; lack of change in objective motor function may reflect under-dosing of therapy; marked gains in subjective function with tDCS warrant further study. This study provided Class II evidence that for children with perinatal stroke and hemiparetic cerebral palsy, the addition of tDCS to moderate-dose motor learning therapy did not significantly improve motor function as
measured by the AHA. The main drawbacks of this phase II clinical trial were: (i) modest sample size \( (n = 24) \), (ii) single-center setting, and (iii) examination of sustainability was limited to 2 months.

### Amyotrophic Lateral Sclerosis

In a review on the diagnosis of amyotrophic lateral sclerosis (ALS), Elman and McCluskey (2010) stated that rTMS remains a largely experimental technique and is not used routinely for clinical diagnosis. In a Cochrane review on rTMS for the treatment of ALS or motor neuron disease, Guo et al (2011) concluded that there is currently insufficient evidence to draw conclusions about the safety and effectiveness of rTMS in the treatment of ALS. They noted that further studies may be helpful if their potential benefit is weighed against the impact of participation in a RCT on people with ALS.

### Autism

In a review on autism, Levy et al (2009) stated that biologically based treatments include anti-infectives, chelation medications, gastro-intestinal medications, hyperbaric oxygen therapy, off-label drugs (e.g., secretin), and intravenous immunoglobulins. Non-biologically based treatments include auditory integration training, chiropractic therapy, cranio-sacral manipulation, facilitated communication, interactive metronome, and transcranial stimulation. However, few studies have addressed the safety and effectiveness of most of these treatments.

### Blepharospasm

In a prospective, randomized, sham-controlled, observer-blinded study, Kranz et al (2010) examined the effects of rTMS on benign essential blepharospasm (BEB). In 12 patients with BEB, these investigators evaluated the effects of a 15-min session of low-frequency (0.2 Hz) rTMS over the anterior cingulate cortex (ACC) with stimulation intensities at 100 % active motor threshold with 3 stimulation coils: (i) a conventional circular coil (C-coil), (ii) a sham coil (S-coil), and (iii) a Hesed coil (H-coil, which allows stimulation of deeper brain regions. Primary outcome was the clinical effects on BEB (blink rate, number of spasms rated by a blinded physician and patient rating before, immediately after, and 1 hour after stimulation); secondary outcome was the blink reflex recovery curve. Subjective stimulation comfort was similar for each coil with no stimulation-associated adverse events. Stimulation with the H- and C-coils resulted in a significant improvement in all 3
outcome measures and was still detectable in physician rating and patient rating 1 hr after stimulation. S-coil stimulation had no effects. The active motor threshold was significantly lower for the H-coil compared to the other 2 coils. The authors concluded that rTMS could be used as a therapeutic tool in BEB. Moreover, they noted that compared to the well-established and long-lasting effects of botulinum toxin and in view of the time-consuming nature of rTMS and its short-lasting effects, it should not be used in routine clinical setting at this stage. Furthermore, they stated that further studies will be necessary to show whether repeated stimulation applications result in lasting clinical effects.

Dementia

Freitas et al (2011) performed a systematic search of all studies using non-invasive stimulation in Alzheimer’s disease (AD) and reviewed all 29 identified articles; 24 focused on measures of motor cortical reactivity and (local) plasticity and functional connectivity, with 8 of these studies assessing also effects of pharmacological agents, and 5 studies focused on the enhancement of cognitive function in AD. Short-latency afferent inhibition (SAI) and resting motor threshold are significantly reduced in AD patients as compared to healthy elders. Results on other measures of cortical reactivity, (e.g., intra-cortical inhibition [ICI]), are more divergent. Acetylcholine-esterase inhibitors and dopaminergic drugs may increase SAI and ICI in AD. Motor cortical plasticity and connectivity are impaired in AD. Transcranial magnetic stimulation/transcranial direct current stimulation (tDCS) can induce acute and short-duration beneficial effects on cognitive function, but the therapeutic clinical significance in AD is unclear. Safety of TMS/tDCS is supported by studies to date. The authors concluded that TMS/tDCS appears safe in AD, but longer-term risks have been insufficiently considered. They stated that TMS holds promise as a physiologic biomarker in AD to identify therapeutic targets and monitor pharmacologic effects. In addition, TMS/tDCS may have therapeutic utility in AD, though the evidence is still very preliminary and cautious interpretation is warranted.

Transcutaneous electrical nerve stimulation (TENS) is the application of an electrical current through electrodes attached to the skin, and is most commonly used for pain relief. It has also been employed for the treatment of a range of neurological and psychiatric conditions such as alcohol and drug dependence, depression, as well as headaches. Transcutaneous electrical nerve stimulation is rarely used for the treatment of dementia. The use of TENS for these indications
entails peripherally applied TENS as well as TENS applied to the head, also known as cranial electrical stimulation (CES). Although several studies suggested that TENS may produce short-lived improvements in some neurological or psychiatric conditions, the limited data from these studies did not allow definite conclusions on the possible benefits of this intervention.

Rose and colleagues (2008) noted that family caregivers of persons with dementia and their care recipients frequently experience sleep and mood disturbances throughout their caregiving and disease trajectories. Because conventional pharmacological treatments of sleep and mood disturbances pose numerous risks and adverse effects to elderly persons, the investigation of other interventions is warranted. As older adults use complementary and alternative medicine interventions for the relief of sleep and mood disturbances, CES may be a viable intervention. These investigators examined the effects of CES on sleep disturbances, depressive symptoms, and caregiving appraisal in spousal caregivers of persons with Alzheimer’s disease (Rose et al, 2009). A total of 38 subjects were randomly assigned to receive active CES or sham CES for 4 weeks. Both intervention groups reported improvement in study measures from baseline scores. A trend toward statistically significant differences in daily sleep disturbances was found between the groups. No differences in depressive symptoms and caregiving appraisal were found between the groups. The authors concluded that these findings did not fully support the efficacy of the short-term use of active CES versus sham CES to improve sleep disturbances, depressive symptoms, or caregiving appraisal.

Guse et al (2010) stated that TMS was introduced as a non-invasive tool for the investigation of the motor cortex. The repetitive application (rTMS), causing longer lasting effects, was used to study the influence on a variety of cerebral functions. High-frequency (greater than 1 Hz) rTMS is known to depolarize neurons under the stimulating coil and to indirectly affect areas being connected and related to emotion and behavior. Researchers found selective cognitive improvement after high-frequency (HF) stimulation specifically over the left dorso-lateral pre-frontal cortex (DLPFC). These researchers performed a systematic review of HF-rTMS studies (1999 to 2009) stimulating over the prefrontal cortex of patients suffering from psychiatric/neurological diseases or healthy volunteers, where the effects on cognitive functions were measured. The cognitive effect was analyzed with regard to the impact of clinical status (patients/healthy volunteers) and stimulation type (verum/sham). Repetitive TMS at 10, 15 or 20 Hz, applied over the left DLPFC,
within a range of 10 to 15 successive sessions and an individual motor threshold of 80 to 110%, is most likely to cause significant cognitive improvement. In comparison, patients tend to reach a greater improvement than healthy participants. Limitations concern the absence of healthy groups in clinical studies and partly the absence of sham groups. Thus, future investigations are needed to assess cognitive rTMS effects in different psychiatric disorders versus healthy subjects using an extended standardized neuropsychological test battery. Since the pathophysiological and neurobiological basis of cognitive improvement with rTMS remains unclear, additional studies including genetics, experimental neurophysiology and functional brain imaging are necessary to explore stimulation-related functional changes in the brain. The authors noted that "[a]ll in all, investigations have to prove the efficacy of rTMS in randomized sham-controlled trials with higher statistical power using larger sample sizes and improved methodology".

Smell and Taste Disorders

Henkin et al (2011) evaluated the effectiveness of rTMS treatment in patients with phantosmia and phantageusia. A total of 17 patients with symptoms of persistent phantosmia and phantageusia with accompanying loss of smell and taste acuity were studied. Before and after treatment, patients were monitored by subjective responses and with psychophysical tests of smell function (olfactometry) and taste function (gustometry). Each patient was treated with rTMS that consisted of 2 sham procedures followed by a real rTMS procedure. After sham rTMS, no change in measurements of distortions or acuity occurred in any patient; after initial real rTMS, 2 patients received no benefit; but in the other 15, distortions decreased and acuity increased. Two of these 15 exhibited total inhibition of distortions and return of normal sensory acuity that persisted for over 5 years of follow-up. In the other 13, inhibition of distortions and improvement in sensory acuity gradually decreased; but repeated rTMS again inhibited their distortions and improved their acuity. Eighty-eight percent of patients responded to this therapeutic method, although repeated rTMS was necessary to induce these positive changes. The authors concluded that these results suggested that rTMS is a potential future therapeutic option to treat patients with the relatively common problems of persistent phantosmia and phantageusia with accompanying loss of taste and smell acuity. Moreover, they stated that additional systematic studies are necessary to confirm these results.
Spinal Cord Injury

Awad et al (2015) reviewed the basic principles and techniques of TMS and provided information and evidence regarding its applications in spinal cord injury (SCI) clinical rehabilitation. A review of the available current and historical literature regarding TMS was conducted, and a discussion of its potential use in SCI rehabilitation is presented. Transcranial magnetic stimulation provides reliable information about the functional integrity and conduction properties of the cortico-spinal tracts and motor control in the diagnostic and prognostic assessment of various neurological disorders. It allows one to follow the evolution of motor control and to evaluate the effects of different therapeutic procedures. Motor-evoked potentials can be useful in follow-up evaluation of motor function during treatment and rehabilitation, specifically in patients with SCI and stroke. Although studies regarding somato-motor functional recovery after SCI have shown promise, more trials are needed to provide strong and substantial evidence. The authors concluded that TMS is a promising non-invasive tool for the treatment of spasticity, neuropathic pain, and somato-motor deficit after SCI. They stated that further investigation is needed to demonstrate whether different protocols and applications of stimulation, as well as alternative cortical sites of stimulation, may induce more pronounced and beneficial clinical effects.

Nardone and colleagues (2014) reviewed the literature on brain neurostimulation techniques in patients with chronic neuropathic pain due to traumatic SCI and evaluated the current evidence for their effectiveness. A MEDLINE search was performed using following terms: "spinal cord injury", "neuropathic pain", "brain stimulation", "deep brain stimulation" (DBS), "motor cortex stimulation" (MCS), "transcranial magnetic stimulation" (TMS), "transcranial direct current stimulation" (tDCS), "cranial electrotherapy stimulation" (CES). Invasive neurostimulation therapies, in particular DBS and epidural MCS, have shown promise as treatments for neuropathic and phantom limb pain. However, the long-term effectiveness of DBS is low, while MCS has a relatively higher potential with lesser complications that DBS. Among the non-invasive techniques, there is accumulating evidence that repetitive TMS can produce analgesic effects in healthy subjects undergoing laboratory-induced pain and in chronic pain conditions of various etiologies, at least partially and transiently. Another very safe technique of non-invasive brain stimulation -- tDCS -- applied over the sensory-motor cortex has been reported to decrease pain sensation and increase pain threshold in healthy subjects. Cranial electrotherapy stimulation has also proved to be effective in
managing some types of pain, including neuropathic pain in subjects with SCI. The authors concluded that a number of studies have begun to use non-invasive neuromodulatory techniques therapeutically to relieve neuropathic pain and phantom phenomena in patients with SCI. Moreover, they stated that further studies are needed to corroborate the early findings and confirm different targets and stimulation paradigms. The utility of these protocols in combination with pharmacological approaches should also be explored.

Moreno-Duarte et al (2014) reviewed initial safety, effectiveness, and potential predictors of response by assessing the effects of neural stimulation techniques to treat SCI pain. A literature search was performed using the PubMed database including studies using the following targeted stimulation strategies: tDCS, high definition tDCS (HD-tDCS), rTMS, CES, TENS, spinal cord stimulation (SCS) and MCS, published prior to June of 2012. These investigators included studies from 1998 to 2012. A total of 8 clinical trials and 1 naturalistic observational study met the inclusion criteria. Among the clinical trials, 3 studies assessed the effects of tDCS, 2 of CES, 2 of rTMS and 1 of TENS. The naturalistic study investigated the analgesic effects of SCS. No clinical trials for epidural MCS or HD-tDCS were found. Parameters of stimulation and also clinical characteristics varied significantly across studies. Three out of 8 studies showed larger effects sizes (0.73, 0.88 and 1.86, respectively) for pain reduction. Classical neuropathic pain symptoms such as dysesthesia (defined as an unpleasant burning sensation in response to touch), allodynia (pain due to a non-painful stimulus), pain in paroxysms, location of SCI in thoracic and lumbar segments and pain in the lower limbs seem to be associated with a positive response to neural stimulation. No significant adverse effects were reported in these studies. The authors concluded that chronic pain in SCI is disabling and resistant to common pharmacologic approaches. Electrical and magnetic neural stimulation techniques have been developed to offer a potential tool in the management of these patients. Although some of these techniques are associated with large standardized mean differences to reduce pain, the authors found an important variability in these results across studies. They stated that there is a clear need for the development of methods to decrease treatment variability and increase response to neural stimulation for pain treatment.

Gao and colleagues (2017) noted that the evidence regarding effectiveness of rTMS on relief of neuropathic pain (NP) in patients with prior SCI is controversial. In a meta-analysis, these researchers evaluated the effectiveness of rTMS in pain...
relieve in patients suffering from SCI associated NP. Medline, PubMed, Cochrane, Embase, Google Scholar databases were searched for clinical studies on effects of rTMS treatment on NP caused by prior SCI published before March 14, 2016 with various combinations of following keywords: transcranial magnetic stimulation, spinal injury, pain. Standardized difference in means with 95 % CI was calculated for the change of pain scores after rTMS or sham rTMS treatments. A total of 2 RCTs and 4 cross-over RCTs were included for the meta-analysis. The RCTs recruited a total of 27 patients. The cross-over RCTs recruited a total of 100 patients. The combined standardized difference in means indicated that patients who received rTMS intervention had better pain relief than those who received sham rTMS intervention, however, the results did not reach statistical significance (STD difference in means = -0.607, 95 % CI: -1.29 to 0.075, p = 0.081). The authors concluded that rTMS might reduce SCI associated neuropathic pain; however, further studies are needed to support this conclusion.

Movement Disorders

Schneider et al (2010) stated that dystonia is associated with impaired somatosensory ability. The electrophysiological method of rTMS can be used for non-invasive stimulation of the human cortex and can alter cortical excitability and associated behavior. Among others, rTMS can alter/improve somatosensory discriminatory abilities, as shown in healthy controls. These researchers applied 5Hz-rTMS over the left primary somatosensory cortex (S1) in 5 patients with right-sided writer's dystonia and 5 controls. They studied rTMS effects on tactile discrimination accuracy and concomitant rTMS-induced changes in hemodynamic activity measured by functional magnetic resonance imaging (fMRI). Before rTMS, patients performed worse on the discrimination task than controls even though fMRI showed greater task-related activation bilaterally in the basal ganglia (BG). In controls, rTMS led to improved discrimination; fMRI revealed this was associated with increased activity of the stimulated S1, bilateral premotor cortex and BG. In dystonia patients, rTMS had no effect on discrimination; fMRI showed similar cortical effects to controls except for no effects in BG. Improved discrimination after rTMS in controls is linked to enhanced activation of S1 and BG. Failure of rTMS to increase BG activation in dystonia may be associated with the lack of effect on sensory discrimination in this group and may reflect impaired processing in BG-S1 connections. Alternatively, the increased BG activation seen in the baseline state without rTMS may reflect a compensatory strategy that saturates a BG contribution to this task.
Traumatic Brain Injury

Demirtas-Tatlidede et al (2012) reviewed novel techniques of non-invasive brain stimulation (NBS), which may have value in assessment and treatment of traumatic brain injury (TBI). Review of the following techniques: TMS, transcranial DCS (tDCS), low-level laser therapy, and transcranial Doppler sonography. Furthermore, these investigators provided a brief overview of TMS studies to date. They described the rationale for the use of these techniques in TBI, discussed their possible mechanisms of action, and raised a number of considerations relevant to translation of these methods to clinical use. Depending on the stimulation parameters, NBS may enable suppression of the acute glutamatergic hyper-excitability following TBI and/or counter the excessive GABAergic effects in the sub-acute stage. In the chronic stage, brain stimulation coupled to rehabilitation may enhance behavioral recovery, learning of new skills, and cortical plasticity. Correlative animal models and comprehensive safety trials seem critical to establish the use of these modalities in TBI. The authors concluded that different forms of NBS techniques harbor the promise of diagnostic and therapeutic utility, particularly to guide processes of cortical re-organization and enable functional restoration in TBI. They noted that future lines of safety research and well-designed clinical trials in TBI are warranted to determine the capability of NBS to promote recovery and minimize disability.

In a double-blind, sham-controlled, cross-over study, Thibaut et al (2014) examined the effects of left dorsolateral prefrontal cortex tDCS (DLPF-tDCS) on Coma Recovery Scale-Revised (CRS-R) scores in severely brain-damaged patients with disorders of consciousness. Anodal and sham tDCS were delivered in randomized order over the left DLPF cortex for 20 minutes in patients in a vegetative state/unresponsive wakefulness syndrome (VS/UWS) or in a minimally conscious state (MCS) assessed at least 1 week after acute traumatic or non-traumatic insult. Clinical assessments were performed using the CRS-R directly before and after anodal and sham tDCS stimulation. Follow-up outcome data were acquired 12 months after inclusion using the Glasgow Outcome Scale-Extended. Patients in MCS (n = 30; interval 43 ± 63 months; 19 traumatic, 11 non-traumatic) showed a significant treatment effect (p = 0.003) as measured by CRS-R total scores. In patients with VS/UWS (n = 25; interval 24 ± 48 months; 6 traumatic, 19 non-traumatic), no treatment effect was observed (p = 0.952). Thirteen (43 %) patients in MCS and 2 (8 %) patients in VS/UWS further showed post-anodal tDCS-related signs of consciousness, which were observed neither during the pre-tDCS
evaluation nor during the pre- or post-sham evaluation (i.e., tDCS responders). Outcome did not differ between tDCS responders and non-responders. The authors concluded that tDCS over left DLPF cortex may transiently improve signs of consciousness in MCS following severe brain damage as measured by changes in CRS-R total scores. Moreover, they stated that the long-term non-invasive neuro-modulatory tDCS outcome clinical improvement in this challenging population remains to be shown.

In an editorial that accompanied the afore-mentioned study, Whyte (2014) stated that “If a longer course of tDCS can accelerate recovery for a subgroup of the DOC population, perhaps a positive response to a single session of tDCS can identify the subgroup of individuals who are treatment responders to this or to other treatments that modulate attention and working memory circuitry. If so, tDCS may provide a useful screening approach for other treatment studies, as well as a useful treatment in its own right”.

In a prospective, case series trial with follow-up at 12 months, Angelakis et al (2014) evaluated the effectiveness of tDCS on improving consciousness in patients with persistent UWS (previously termed persistent vegetative state [PVS]) or in a MCS. Inpatients in a PVS/UWS or MCS (n = 10; 7 men, 3 women; age range of 19 to 62 years; etiology: traumatic brain injury, n = 5; anoxia, n = 4; post-operative infarct, n = 1; duration of PVS/UWS or MCS range of 6 months to 10 years). No participant withdrew because of adverse effects. All patients received sham tDCS for 20 minutes per day, 5 days per week, for 1 week, and real tDCS for 20 minutes per day, 5 days per week, for 2 weeks. An anodal electrode was placed over the left primary sensorimotor cortex or the left DLPF, with cathodal stimulation over the right eyebrow. One patient in an MCS received a second round of 10 tDCS sessions 3 months after initial participation. Main outcome measure was JFK Coma Recovery Scale-Revised. All patients in an MCS showed clinical improvement immediately after treatment. The patient who received a second round of tDCS 3 months after initial participation showed further improvement and emergence into consciousness after stimulation, with no change between treatments. One patient who was in an MCS for less than 1 year before treatment (post-operative infarct) showed further improvement and emergence into consciousness at 12-month follow-up. No patient showed improvement before stimulation. No patient in a PVS/UWS showed immediate improvement after stimulation, but 1 patient who was in a PVS/UWS for 6 years before treatment showed improvement and change of status to an MCS at 12-month follow-up. The authors concluded that tDCS seems
promising for the rehabilitation of patients with severe disorders of consciousness; severity and duration of pathology may be related to the degree of tDCS' beneficial effects.

Addiction

Gorelick et al (2014) noted that TMS is still in the early stages of study as addiction treatment. These researchers identified 19 human studies using rTMS to manipulate drug craving or use, which exposed a total of 316 adults to active rTMS. Nine studies involved tobacco, 6 alcohol, 3 cocaine, and 1 methamphetamine. The majority of studies targeted high-frequency (5 to 20 Hz; expected to stimulate neuronal activity) rTMS pulses to the dorsolateral prefrontal cortex. Only 5 studies were controlled clinical trials: 2 of 4 nicotine trials found decreased cigarette smoking; the cocaine trial found decreased cocaine use. Many aspects of optimal treatment remain unknown, including rTMS parameters, duration of treatment, relationship to cue-induced craving, and concomitant treatment. The mechanisms of rTMS potential therapeutic action in treating addictions are poorly understood, but may involve increased dopamine and glutamate function in cortico-mesolimbic brain circuits and modulation of neural activity in brain circuits that mediate cognitive processes relevant to addiction, such as response inhibition, selective attention, and reactivity to drug-associated cues. The authors concluded that rTMS treatment of addiction must be considered experimental at this time, but appears to have a promising future.

Makani and associates (2017) stated that addiction and related disorders are devastating with their tremendous social, psychological, and physical consequences for which development of optimally effective treatments are long overdue; rTMS is relatively safe and is becoming an emerging therapeutic tool for these conditions. These investigators carried out a systematic review using PubMed, PsycINFO, PsychiatryOnline and Cochrane Library ranging from year 2001 to 2017. They retrieved 70 related articles of which, based on the Strength of Recommendation Taxonomy (SORT) guidelines, 33 indicated Level-1 study quality and class-B strength of recommendation for rTMS in nicotine addiction (effective in 218/289 subjects who received rTMS as found in 11 studies). Level-2/Class-B evidence was found for alcohol and cocaine addictions (alcohol: effective in 126/193 subjects who received rTMS as found in 8 studies; cocaine: effective in 86/128 subjects, as found in 5 studies). For food cravings, Level-3/Class-B evidence was noted (effective in 134/169, found in 7 studies). However, the
evidence was limited to Level-3/Class-C for heroin (10/20 subjects received active rTMS, effective in 1 study), methamphetamine (33/48 subjects received active rTMS, effective in 2 studies), cannabis (18/18 subjects received active rTMS, effective in 1 study), and pathological gambling (31/31 subjects received active rTMS, effective in 2 studies). The authors concluded that rTMS may serve as an emerging therapeutic option for addiction and related disorders. The major voids in this field include important methodological limitations and dearth of knowledge about precise mechanism of action that need to be addressed in the future studies.

**Congenital Hemiparesis**

In a phase I randomized, double-blinded, placebo-controlled pre-test/post-test trial, Gillick et al (2015) investigated the safety of combining a 6-Hz primed low-frequency rTMS intervention in the contralesional hemisphere with a modified constraint-induced movement therapy (mCIMT) program in children with congenital hemiparesis. Subjects (n = 19; age range of 8 to 17 years) with congenital hemiparesis caused by ischemic stroke or peri-ventricular leukomalacia. No subject withdrew because of adverse events. All subjects included completed the study. Subjects were randomized to 1 of 2 groups: (i) either real rTMS plus mCIMT (n = 10) or (ii) sham rTMS plus mCIMT (n = 9). Main outcome measures included adverse events, physician assessment, ipsilateral hand function, stereognosis, cognitive function, subject report of symptoms assessment, and subject questionnaire. No major adverse events occurred. Minor adverse events were found in both groups. The most common events were headaches (real: 50 %, sham: 89 %; p = 0.14) and cast irritation (real: 30 %, sham: 44 %; p = 0.65). No differences between groups in secondary cognitive and unaffected hand motor measures were found. The authors concluded that primed rTMS can be used safely with mCIMT in congenital hemiparesis. They provided new information on the use of rTMS in combination with mCIMT in children. They stated that these findings could be useful in research and future clinical applications in advancing function in congenital hemiparesis.

**Communication and Swallowing Disorders**

Gadenz et al (2015) systematically review RCTs that evaluated the effects of rTMS on rehabilitation aspects related to communication and swallowing functions. A search was conducted on PubMed, Clinical Trials, Cochrane Library, and ASHA electronic databases. Studies were judged according to the eligibility criteria and
analyzed by 2 independent and blinded researchers. These researchers analyzed 9 studies: 4 about aphasia, 3 about dysphagia, 1 about dysarthria in Parkinson's disease and 1 about linguistic deficits in Alzheimer's disease. All aphasia studies used low-frequency rTMS to stimulate Broca's homologous area. High-frequency rTMS was applied over the pharyngo-esophageal cortex from the left and/or right hemisphere in the dysphagia studies and over the left dorso-lateral prefrontal cortex in the Parkinson's and Alzheimer's studies. Two aphasia and all dysphagia studies showed a significant improvement of the disorder, compared to the sham group. The other 2 studies related to aphasia found a benefit restricted to subgroups with a severe case or injury on the anterior portion of the language cortical area, respectively, whereas the Alzheimer's study demonstrated positive effects specific to auditory comprehension. There were no changes for vocal function in the Parkinson's study. The authors concluded that the benefits of the technique and its applicability in neurogenic disorders related to communication and deglutition are still uncertain; other RCTs are needed to clarify the optimal stimulation protocol for each disorder studied and its real effects.

Epilepsy

Zeiler et al (2015) performed a systematic review on the use of rTMS in the treatment of status epilepticus (SE) and refractory status epilepticus (RSE). MEDLINE, BIOSIS, EMBASE, Global Health, Healthstar, Scopus, Cochrane Library, the International Clinical Trials Registry Platform, clinicaltrials.gov (inception to August 2015), and gray literature were searched. The strength of evidence was adjudicated using Oxford and GRADE methodology. These investigators identified 11 original articles; 21 patients were described, with 13 adult and 8 pediatric. All studies were retrospective. Seizure reduction/control with rTMS occurred in 15 of the 21 patients (71.4 %), with 5 (23.8 %) and 10 (47.6 %) displaying partial and complete responses, respectively. Seizures recurred after rTMS in 73.3 % of the patients who had initially responded. All studies were an Oxford level 4, GRADE D level of evidence. The authors concluded that Oxford level 4, GRADE D evidence exists to suggest a potential impact on seizure control with the use of rTMS for FSE and FRSE, though durability of the therapy is short-lived. They stated that routine use of rTMS in this context cannot be recommended at this time; and further prospective study of this intervention is needed.
Pereira et al (2016) noted that about 1/3 of patients with epilepsy remain with pharmacologically intractable seizures. An emerging therapeutic modality for seizure suppression is rTMS. Despite being considered a safe technique, rTMS carries the risk of inducing seizures, among other milder adverse events, and thus, its safety in the population with epilepsy should be continuously assessed. These researchers performed an updated systematic review on the safety and tolerability of rTMS in patients with epilepsy, similar to a previous report published in 2007, and estimated the risk of seizures and other adverse events during or shortly after rTMS application. They searched the literature for reports of rTMS being applied on patients with epilepsy, with no time or language restrictions, and obtained studies published from January 1990 to August 2015. A total of 46 publications were identified, of which 16 were new studies published after the previous safety review of 2007. Thee investigators noted the total number of subjects with epilepsy undergoing rTMS, medication usage, incidence of adverse events, and rTMS protocol parameters: frequency, intensity, total number of stimuli, train duration, inter-train intervals, coil type, and stimulation site. Their main data analysis included separate calculations for crude per subject risk of seizure and other adverse events, as well as risk per 1,000 stimuli. They also performed an exploratory, secondary analysis on the risk of seizure and other adverse events according to the type of coil used (figure-of-8 or circular), stimulation frequency (less than or equal to 1Hz or greater than 1Hz), pulse intensity in terms of motor threshold (less than 100 % or greater than or equal to 100 %), and number of stimuli per session (less than 500 or greater than or equal to 500). Presence or absence of adverse events was reported in 40 studies (n = 426 subjects). A total of 78 (18.3 %) subjects reported adverse events, of which 85 % were mild. Headache or dizziness was the most common one, occurring in 8.9 %. These researchers found a crude per subject seizure risk of 2.9 % (95 % CI: 1.3 to 4.5), given that 12 subjects reported seizures out of 410 subjects included in the analysis after data of patients with epilepsia partialis continua or status epilepticus were excluded from the estimate. Only 1 of the reported seizures was considered atypical in terms of the clinical characteristics of the patients' baseline seizures. The atypical seizure happened during high-frequency rTMS with maximum stimulator output for speech arrest, clinically arising from the region of stimulation. Although these investigators estimated a larger crude per subject seizure risk compared with the previous safety review, the corresponding CIs contained both risks. Furthermore, the exclusive case of atypical seizure was the same as reported in the previous report. The authors concluded that the risk of seizure induction in patients with epilepsy undergoing rTMS was small and that the risk of other adverse events was similar to...
that of rTMS applied to other conditions and to healthy subjects. They stated that these findings should be interpreted with caution, given the need for adjusted analysis controlling for potential confounders, such as baseline seizure frequency. Moreover, they noted that the similarity between the safety profiles of rTMS applied to the population with epilepsy and to individuals without epilepsy supports further investigation of rTMS as a therapy for seizure suppression.

In a Cochrane review, Chen and colleagues (2016) evaluated the evidence for the use of TMS in individuals with drug-resistant epilepsy compared with other available treatments in reducing seizure frequency, improving quality of life, reducing epileptiform discharges, antiepileptic medication use, and side-effects. The authors judged the quality of evidence for the primary outcomes of this review to be low. There is evidence that rTMS is safe and not associated with any adverse events, but given the variability in technique and outcome reporting that prevented meta-analysis, the evidence for efficacy of rTMS for seizure reduction is still lacking despite reasonable evidence that it is effective at reducing epileptiform discharges.

Navigated Transcranial Magnetic Stimulation:

Navigated TMS is being studied as a diagnostic tool to stimulate functional cortical areas at precise anatomical locations to induce measurable responses. This technology is being investigated to map functionally essential motor areas for diagnostic purposes and for treatment planning.

Navigated TMS is a novel tool for pre-operative functional mapping. It has been used for motor mapping in the vicinity of rolandic brain lesions as well as for mapping human language areas.

Rossini and Rossi (2007) stated that TMS is widely used in clinical neurophysiology, including rehabilitation and intra-operative monitoring. Single-pulse TMS and other more recent versions (e.g., paired-pulse TMS, rTMS, integration with structural and functional MRI, and neuro-navigation) allow motor output to be mapped precisely to a given body district. Moreover, TMS can be used to assess excitatory/inhibitory intra-cortical circuits and to provide information on brain physiology and pathophysiology of various neuropsychiatric diseases as well as on the mechanisms of brain plasticity and of neuroactive drugs. Transcranial magnetic stimulation applied over non-motor areas made it possible to extend research applications in several fields of psychophysiology. Being able to
induce relatively long-lasting excitability changes, rTMS has made the treatment of neuropsychiatric diseases linked with brain excitability dysfunctions possible. The authors noted that these uses, however, warrant further large-scale studies. In emerging fields of research, TMS-EEG co-registration is considered a promising approach to evaluate cortico-cortical connectivity and brain reactivity with high temporal resolution. However, safety and ethical limitations of TMS technique need a high level of vigilance.

Picht et al (2011) compared the accuracy of a 3-dimensional MRI-navigated TMS system with the gold standard of direct cortical stimulation. The primary motor areas of 20 patients with rolandic tumors were mapped pre-operatively with navigated TMS at 110% of the individual resting motor threshold. Intra-operative direct cortical stimulation was available from 17 patients. The stimulus locations eliciting the largest electromyographic response in the target muscles (“hotspots”) were determined for both methods. The navigated TMS and direct cortical stimulation hotspots were located on the same gyrus in all cases. The mean +/- SEM distance between the navigated TMS and direct cortical stimulation hotspots was 7.83 +/- 1.18 mm for the abductor pollicis brevis (APB) muscle (n = 15) and 7.07 +/- 0.88 mm for the tibialis anterior (TA) muscle (n = 8). When a low number of direct cortical stimulations was performed, the distance between the navigated TMS and direct cortical stimulation hotspots increased substantially (r = -0.86 for APB). After exclusion of the cases with less than 15 direct cortical stimulation APB responses, the mean +/- SEM distance between the hotspots was only 4.70 +/- 1.09 mm for APB (n = 8). The authors concluded that peri-tumoral mapping of the motor cortex by navigated TMS agreed well with the gold standard of direct cortical stimulation. Thus, navigated TMS is a reliable tool for pre-operative mapping of motor function. These preliminary findings need to be validated by well-designed studies with larger number of participants.

Picht et al (2012) evaluated how much influence, benefit, and impact navigated TMS has on the surgical planning for tumors near the motor cortex. This study reviewed the records of 73 patients with brain tumors in or near the motor cortex, mapped pre-operatively with navigated TMS. The surgical team prospectively classified how much influence the navigated TMS results had on the surgical planning. Step-wise regression analysis was used to explore which factors predict the amount of influence, benefit, and impact navigated TMS has on the surgical planning. The influence of navigated TMS on the surgical planning was as follows: it confirmed the expected anatomy in 22% of patients, added knowledge that was
not used in 23 %, added awareness of high-risk areas in 27 %, modified the approach in 16 %, changed the planned extent of resection in 8 %, and changed the surgical indication in 3 %. The authors concluded that navigated TMS had an objective benefit on the surgical planning in 25 % of the patients and a subjective benefit in an additional 50 % of the patients. It had an impact on the surgery itself in just more than 50 % of the patients.

Krieg et al (2012) stated that navigated TMS is a newly evolving technique. Despite its supposed purpose (e.g., pre-operative central region mapping), little is known about its accuracy compared with established modalities like direct cortical stimulation and functional MR imaging (fMRI). These researchers compared the accuracy of navigated TMS with direct cortical stimulation and fMRI. Fourteen patients with tumors in or close to the pre-central gyrus were examined using navigated TMS for motor cortex mapping, as were 12 patients with lesions in the subcortical white matter motor tract. Moreover, pre-operative fMRI and intra-operative mapping of the motor cortex were performed via direct cortical stimulation, and the outlining of the motor cortex was compared. In the 14 cases of lesions affecting the pre-central gyrus, the primary motor cortex as outlined by navigated TMS correlated well with that delineated by intra-operative direct cortical stimulation mapping, with a deviation of 4.4 +/- 3.4 mm between the 2 methods. In comparing navigated TMS with fMRI, the deviation between the 2 methods was much larger: 9.8 +/- 8.5 mm for the upper extremity and 14.7 +/- 12.4 mm for the lower extremity. In 13 of 14 cases, the surgeon admitted easier identification of the central region because of navigated TMS. The procedure had a subjectively positive influence on the operative results in 5 cases and was responsible for a changed resection strategy in 2 cases. One of 26 patients experienced navigated TMS as unpleasant; none found it painful. The authors concluded that navigated TMS correlates well with direct cortical stimulation as a gold standard despite factors that are supposed to contribute to the inaccuracy of navigated TMS. Moreover, surgeons have found navigated TMS to be an additional and helpful modality during the resection of tumors affecting eloquent motor areas, as well as during pre-operative planning. These findings need to be confirmed.

Frey et al (2012) established a novel approach for fiber tracking based on navigated TMS mapping of the primary motor cortex and proposed a new algorithm for determination of an individualized fractional anisotropy value for reliable and objective fiber tracking. A total of 50 patients (22 females, 28 males; median age of 58 years, range of 20 to 80) with brain tumors compromising the primary motor
cortex and the cortico-spinal tract underwent pre-operative MRI and navigated TMS
mapping. Stimulation spots evoking muscle potentials (MEP) closest to the tumor
were imported into the fiber tracking software and set as seed points for
tractography. Next the individual FA threshold, namely, the highest FA value
leading to visualization of tracts at a pre-defined minimum fiber length of 110 mm,
was determined. Fiber tracking was then performed at a fractional anisotropy value
of 75 % and 50 % of the individual FA threshold. In addition, fiber tracking
according to the conventional knowledge-based approach was performed. Results
of tractography of either method were presented to the surgeon for pre-operative
planning and integrated into the navigation system and its impact was rated using a
questionnaire. Mapping of the motor cortex was successful in all patients. A
fractional anisotropy threshold for cortico-spinal tract reconstruction could be
obtained in every case. TMS-based results changed or modified surgical strategy
in 23 of 50 patients (46 %), whereas knowledge-based results would have changed
surgical strategy in 11 of 50 patients (22 %). Tractography results facilitated intra-
operative orientation and electrical stimulation in 28 of 50 (56 %) patients. Tracking
at 75 % of the individual FA thresholds was considered most beneficial by the
respective surgeons. The authors concluded that fiber tracking based on navigated
TMS by the proposed standardized algorithm represents an objective visualization
method based on functional data and provides a valuable instrument for pre-
operative planning and intra-operative orientation and monitoring. This was a small
study and it did not validate navigated TMS findings with improved health
outcomes.

Tarapore et al (2012) noted that direct cortical stimulation is the gold-standard
technique for motor mapping during craniotomy. However, pre-operative non-
invasive motor mapping is becoming increasingly accurate. Two such non-invasive
modalities are navigated TMS and magnetoencephalography (MEG) imaging.
These investigators compared the accuracy of TMS to both direct cortical
stimulation and MEG imaging. Patients with tumors in proximity to primary motor
cortex underwent pre-operative TMS and MEG imaging for motor mapping. The
patients subsequently underwent motor mapping via intra-operative direct cortical
stimulation. The loci of maximal response were recorded from each modality and
compared. Motor strength was assessed at 3 months post-operatively.
Transcranial magnetic stimulation and MEG imaging were performed on 24
patients. Intra-operative direct cortical stimulation yielded 8 positive motor sites in 5
patients. The median distance +/- SEM between TMS and direct cortical
stimulation motor sites was 2.13 +/- 0.29 mm, and between TMS and MEG imaging

http://www.aetna.com/cpb/medical/data/400_499/0469.html 03/28/2019
motor sites was 4.71 +/- 1.08 mm. In no patients did direct cortical stimulation
motor mapping reveal a motor site that was unrecognized by TMS. Three of 24
patients developed new, early neurological deficit in the form of upper-extremity
paresis. At the 3-month follow-up evaluation, 2 of these patients were significantly
improved, experiencing difficulty only with fine motor tasks; the remaining patient
had improvement to 4/5 strength. There were no deaths over the course of the
study. The authors concluded that maps of the motor system generated with TMS
correlate well with those generated by both MEG imaging and direct cortical
stimulation. Negative TMS mapping also correlates with negative direct cortical
stimulation mapping.

In a feasibility study, Forster et al (2012) examined cortical motor representation
after resection of peri-rolandic World Health Organization grade II and III gliomas
using navigated TMS. A total of 5 patients were examined before neurosurgery
and after a follow-up period of 17.7 +/- 6.8 months. As a control, 5 healthy age-
matched subjects were equally studied by navigated TMS in 2 sessions spaced
12.6 (range of 2 to 35) days apart. Resting motor thresholds (RMT), hotspots and
centers of gravity (CoG) were identified for the first dorsal interosseous (FDI), APB,
extensor digitorum (EXT), TA and abductor hallucis (AH) muscles. Euclidian
distances, coefficients of variance and intra-class correlation coefficients (ICC)
were calculated. Healthy subjects showed moderate-to-excellent reliability
measurement of RMT (ICC = 0.69 to 0.94). Average displacement of CoGs across
sessions was 0.68 +/- 0.34 cm in the dominant and 0.76 +/- 0.38 cm in the non-
dominant hemisphere; hotspots moved 0.87 +/- 0.51 cm and 0.83 +/- 0.45 cm,
respectively. In 1 patient these parameters differed significantly from the control
group (p < 0.05 for both CoGs and hotspots). Overall, all patients’ CoGs moved
1.12 +/- 0.93 cm, and hotspots were 1.06 +/- 0.7 cm apart. In both patients and
healthy subjects, movement of assessed parameters was more important along the
X- than the Y-axis. The authors concluded that navigated TMS allows evaluating
cortical re-organization after brain tumor surgery. It may contribute to the
understanding of neurofunctional dynamics, thus influencing therapeutic strategy.

Makela et al (2013) stated that navigated TMS has been suggested to be useful in
pre-operative functional localization of motor cortex in patients having tumors close
to the somato-motor cortex. These researchers described functional plasticity of
motor cortex indicated by navigated TMS in 2 patients with epilepsy. Navigated
TMS, fMRI, diffusion-tensor (DT)-tractography and MEG were utilized to pre-
operatively localize motor cortical areas in the work-up for epilepsy surgery. The
localizations were compared with each other, with the cortical anatomical landmarks, and in 1 patient with invasive electrical cortical stimulation (ECS). In 2 out of 19 studied patients, navigated TMS identified motor cortical sites that differed from those indicated by anatomical landmarks. In 1 patient, navigated TMS activated preferentially premotor cortex rather than pathways originating from the pre-central gyrus. Functional MRI and MEG localizations conformed with navigated TMS whereas ECS localized finger motor function into the pre-central gyrus.

Resection of the area producing motor responses in biphasic navigated TMS did not produce a motor deficit. In the other patient, navigated TMS indicated abnormal ipsilateral hand motor cortex localization and confirmed the functionality of aberrant motor cortical representations of the left foot also indicated by fMRI and DT-tractography. The authors concluded that navigated TMS may reveal the functional plasticity and shifts of motor cortical function. Epileptic foci may modify cortical inhibition and the navigated TMS results. Thus, the authors noted that in some patients with epilepsy, the navigated TMS results need to be interpreted with caution with regard to surgical planning.

In summary, there is insufficient evidence from peer-reviewed medical literature that navigated TMS is an effective clinical diagnostic test. Most published studies entailed small number of subjects; well-designed studies with larger sample sizes are needed to ascertain how this test can reduce clinical diagnostic uncertainty or impact treatment planning.

**Obsessive-Compulsive Disorder**

Trevizol and colleagues (2016) stated that TMS is a promising non-invasive brain stimulation intervention; it has been proposed for OCD with auspicious results. These investigators assessed the effectiveness of TMS for OCD in RCTs. They performed a systematic review using Medline and Embase from the first RCT available until March 11, 2016. The main outcome was the Hedges g for continuous scores for Yale-Brown Obsessive Compulsive Scale in a random-effects model. Heterogeneity was evaluated with the I and the χ test. Publication bias was evaluated using the Begg funnel plot. Meta-regression was performed using the random-effects model modified by Knapp and Hartung. These researchers included 15 RCTs (n = 483), most had small-to-modest sample sizes. Comparing active versus sham TMS, active stimulation was significantly superior for OCD symptoms (Hedges g = 0.45; 95% CI: 0.2 to 0.71). The funnel plot showed that the risk of publication bias was low and between-study heterogeneity was low (I =
Meta-regression showed no particular influence of any variable on the results. The authors concluded that TMS was superior to sham stimulation for the amelioration of OCD symptoms; trials had moderate heterogeneity results, despite different protocols of stimulation used. They stated that further RCTs with larger sample sizes are needed to clarify the precise impact of TMS in OCD symptoms.

Restless Legs Syndrome

The American Academy of Neurology (AAN)’s practice guideline on “Treatment of restless legs syndrome” (Winkelman et al, 2016) stated that “rTMS is possibly effective in the treatment of primary moderate to severe RLS …. Cathodal and anodal transcranial direct current stimulation are probably ineffective for improving RLS symptoms in women with RLS who were drug-naive”. It stated that “When non-pharmacologic approaches are desired, clinicians should consider prescribing pneumatic compression (Level B) and may consider prescribing near-infrared spectroscopy or transcranial magnetic stimulation (Level C)”.

Furthermore, an UpToDate review on “Treatment of restless legs syndrome/Willis-Ekbom disease and periodic limb movement disorder in adults” (Tarsy and Silber, 2017) does not mention transcranial magnetic stimulation and cranial direct electrical stimulation as therapeutic options.

Visual Hallucinations after Stroke

Rafique and colleagues (2016) examined the effectiveness of multi-day rTMS to the occipital cortex in a patient with continuous visual phosphene hallucinations for more than 2 years following occipital stroke. Low-frequency rTMS (1 Hz) was applied to the lesion site for 30 minutes daily over 5 consecutive days; fMRI was performed before and after rTMS treatment. Increased application of rTMS corresponded with a reduction in intensity of visual phosphene hallucinations and was reflected in altered blood oxygen level-dependent signal; fMRI revealed focal excitatory discharges at the border of the lesion, highlighting the origin of phosphenes. Post-rTMS, rTMS did not simply suppress activity in the patient but rather re-distributed the previously imbalanced cortical activity not only at the stimulation site but in remote cortical regions so that it more closely resembled that of controls. The authors concluded that this case was rare in its presentation of chronic continuous visual phosphene hallucinations following occipital stroke. They
presented a case of multi-day application of rTMS to visual cortex and demonstrated that rTMS provided a valuable therapeutic intervention in modulating visual hallucinations following occipital damage. This study provided Class IV evidence in a single-case report that multi-day rTMS reduced intra-hemispheric and inter-hemispheric imbalance and associated visual phosphene hallucinations following occipital stroke. The main drawbacks of this study were: (i) single-case design, and (ii) the inability to refine stimulation intensity and duration to attain maximal phosphine suppression.

Differential Diagnosis of Alzheimer Disease from Frontotemporal Dementia:

Benussi and colleagues (2017) examined if a TMS multi-paradigm approach can be used to distinguish AD from frontotemporal dementia (FTD). Paired-pulse TMS was used to investigate short-interval intra-cortical inhibition (SICI) and facilitation (ICF), long-interval intra-cortical inhibition, and short-latency afferent inhibition (SAI) to measure the activity of different intra-cortical circuits in patients with AD, patients with FTD, and healthy controls (HC). The primary outcome measures were sensitivity and specificity of TMS measures, derived from receiver operating curve analysis. A total of 175 participants met the inclusion criteria. These researchers diagnosed 79 patients with AD, 64 patients with FTD, and 32 HC. They found that while patients with AD were characterized by a specific impairment of SAI, FTD showed a remarkable dysfunction of SICI-ICF intra-cortical circuits. With the use of the best indexes, TMS differentiated FTD from AD with a sensitivity of 91.8 % and specificity of 88.6 %, AD from HC with a sensitivity of 84.8 % and specificity of 90.6 %, and FTD from HC with a sensitivity of 90.2 % and specificity of 78.1 %. These results were confirmed in patients with mild disease. The authors concluded that TMS is a non-invasive procedure that reliably distinguishes AD from FTD and HC and, if these findings are replicated in larger studies, could represent a useful additional diagnostic tool for clinical practice. This study provided Class III evidence that TMS measures can distinguish patients with AD from those with FTD. These researchers stated that further studies should examine if the AD/FTD-specific pattern of cortical dysfunction, classified according to the SICI-ICF/SAI ratio identified here, could also provide relevant prognostic information. The SICI-ICF/SAI measure has been shown to provide the footprints of the specific underlying neurotransmitter deficit, having the potential to be used as an additional diagnostic instrument in clinical practice and eventually in clinical trials.
Treatment of Complex Regional Pain Syndrome:

Nardone and colleagues (2018) noted that the sensory and motor cortical representation corresponding to the affected limb is altered in patients with complex regional pain syndrome (CRPS). In this review, these investigators performed a systematic search of all studies using TMS to explore cortical excitability/plasticity and rTMS for the treatment of CRPS. Literature searches were conducted using PubMed and Embase. They identified 8 articles matching the inclusion criteria; 114 patients (76 females and 38 males) were included in these studies. Most of them have applied TMS in order to physiologically characterize CRPS type I. Changes in motor cortex excitability and brain mapping have been reported in CRPS-I patients. Sensory and motor hyper-excitability were in the most studies bilateral and likely involve corresponding regions within the central nervous system (CNS) rather than the entire hemisphere. Conversely, sensorimotor integration and plasticity were found to be normal in CRPS-I. TMS examinations also revealed that the nature of motor dysfunction in CRPS-I patients differed from that observed in patients with functional movement disorders, limb immobilization, or idiopathic dystonia. TMS studies may thus lead to the implementation of correct rehabilitation strategies in CRPS-I patients; 2 studies have begun to therapeutically use rTMS. The authors concluded that this non-invasive brain stimulation approach could have therapeutic utility in CRPS, but further well-designed studies are needed to corroborate initial findings.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>90867</td>
<td>Therapeutic repetitive transcranial magnetic stimulation treatment; planning</td>
</tr>
<tr>
<td>90868</td>
<td>delivery and management, per session</td>
</tr>
<tr>
<td>90869</td>
<td>subsequent motor threshold re-determination with delivery and management</td>
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</table>

CPT Codes not covered for indications listed in the CPB:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td>0310T</td>
<td>Motor function mapping using non-invasive navigated transcranial magnetic stimulation (nTMS) for therapeutic treatment planning, upper and lower extremity</td>
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</table>

HCPCS codes covered for indications listed in the CPB:

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<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>G0295</td>
<td>Electromagnetic therapy, to one or more areas</td>
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ICD-10 codes covered if selection criteria are met:

<table>
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<tr>
<th>Code</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>F32.2 - F32.3</td>
<td>Major depressive disorder, single episode, severe without/with psychotic features</td>
</tr>
<tr>
<td>F33.2 - F33.3</td>
<td>Major depressive disorder, recurrent, severe without/with psychotic features</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>C71.0 - C71.9</td>
<td>Malignant neoplasm of brain</td>
</tr>
<tr>
<td>D33.0 - D33.2</td>
<td>Benign neoplasm of brain</td>
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<tr>
<td>F01.50 - F32.1, F32.4 - F33.1, F33.40 - F99</td>
<td>Mental and behavioral disorders</td>
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<tr>
<td>G11.4</td>
<td>Hereditary spastic paraplegia</td>
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<tr>
<td>G12.21</td>
<td>Amyotrophic lateral sclerosis</td>
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<tr>
<td>G20</td>
<td>Parkinson's disease</td>
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<tr>
<td>G21.4</td>
<td>Vascular parkinsonism</td>
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<tr>
<td>G24.3</td>
<td>Spasmodic torticollis</td>
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<td>G24.5</td>
<td>Blepharospasm</td>
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<td>G25.81</td>
<td>Restless legs syndrome</td>
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<tr>
<td>G30.0 - G30.9</td>
<td>Alzheimer's disease</td>
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<tr>
<td>G31.0 - G31.9</td>
<td>Frontotemporal dementia</td>
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<td>G40.0 - G40.919</td>
<td>Epilepsy and recurrent seizures</td>
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<td>G43.001 - G43.919</td>
<td>Migraine</td>
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<td>G44.001 - G44.89</td>
<td>Other headaches syndromes</td>
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<tr>
<td>G47.00 - G47.9</td>
<td>Sleep disorders</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>-------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>G54.6 - G54.7</td>
<td>Phantom limb syndrome [associated with spinal cord injury]</td>
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<tr>
<td>G80.8</td>
<td>Other cerebral palsy [congenital hemiparesis]</td>
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<td>G81.10 - G81.14</td>
<td>Spastic hemiplegia</td>
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<tr>
<td>G89.0</td>
<td>Central pain syndrome [post stroke]</td>
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<td>G90.50 - G90.59</td>
<td>Complex regional pain syndrome I (CRPS I)</td>
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<td>H53.40</td>
<td>Unspecified visual field defects.</td>
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<tr>
<td>H93.11 - H93.19</td>
<td>Tinnitus</td>
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<td>I69.020 -</td>
<td>Aphasia, dysphasia, dysarthria, fluency disorders and other speech and</td>
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<tr>
<td>I69.028</td>
<td>language deficits following nontraumatic subarachnoid hemorrhage</td>
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<td>I69.120 - 69.128</td>
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<tr>
<td></td>
<td>language deficits following nontraumatic intracerebral hemorrhage</td>
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<tr>
<td>I69.220 -</td>
<td>Aphasia, dysphasia, dysarthria, fluency disorders and other speech and</td>
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<tr>
<td>I69.228</td>
<td>language deficits following nontraumatic intracranial hemorrhage</td>
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<td>I69.320 -</td>
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<td>I69.328</td>
<td>language deficits following cerebral infarction</td>
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<td>I69.820 -</td>
<td>Aphasia, dysphasia, dysarthria, fluency disorders and other speech and</td>
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<tr>
<td>I69.828</td>
<td>language deficits following other cerebrovascular disease</td>
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<td>I69.920 -</td>
<td>Aphasia, dysphasia, dysarthria, fluency disorders and other speech and</td>
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<tr>
<td>I69.928</td>
<td>language deficits following unspecified cerebrovascular disease</td>
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<td>J38.5</td>
<td>Laryngeal spasm</td>
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<td>K22.0</td>
<td>Achalasia of cardia</td>
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<td>K22.4</td>
<td>Dyskinesia of esophagus</td>
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<td>K31.3</td>
<td>Pylorospasm, not elsewhere classified</td>
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<tr>
<td>K59.4</td>
<td>Anal spasm</td>
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<tr>
<td>K83.4</td>
<td>Spasm of sphincter of Oddi</td>
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<td>M54.10 -</td>
<td>Radiculopathy</td>
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<td>M54.18</td>
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<tr>
<td>M60.811 -</td>
<td>Myositis</td>
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<tr>
<td>M60.9</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<td>--------------</td>
<td>-------------------------------------------------------</td>
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<tr>
<td>M62.40 - M62.49</td>
<td>Contracture of muscle</td>
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<tr>
<td>M62.830 - M62.838</td>
<td>Muscle spasm</td>
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<tr>
<td>M79.1</td>
<td>Myalgia</td>
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<tr>
<td>M79.2</td>
<td>Neuralgia and neuritis, unspecified</td>
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<td>R25.0 - R25.9</td>
<td>Abnormal involuntary movements</td>
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<td>R27.0 - R27.9</td>
<td>Other lack of coordination</td>
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<td>R43.0 - R43.9</td>
<td>Disturbances of smell and taste</td>
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<tr>
<td>R44.0</td>
<td>Auditory hallucinations</td>
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<td>R47.01</td>
<td>Aphasia</td>
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<td>R47.02</td>
<td>Dysphasia</td>
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<tr>
<td>R47.1</td>
<td>Dysarthria and anarthria</td>
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<tr>
<td>R51</td>
<td>Headache</td>
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<td>S06.0x0+ - S06.9x9+</td>
<td>Intracranial injury [traumatic brain injury]</td>
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<tr>
<td>S12.000+ - S12.691+</td>
<td>Fracture of vertebral column [must be billed with codes for spinal cord injury]</td>
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<td>S22.000+ - S22.089+</td>
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<td>S32.000+ - S32.2xx+</td>
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</tr>
<tr>
<td>S14.101+ - S14.159+</td>
<td>Spinal cord injury</td>
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<td>S24.101+ - S24.159+</td>
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<tr>
<td>S34.101+ - S34.139+</td>
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Cranial Electrical Stimulation:

CPT codes not covered for indications listed in the CPB:

| 64550 | Application of surface (transcutaneous) neurostimulator |

HCPCS codes not covered for indications listed in the CPB:
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4556</td>
<td>Electrodes (e.g., apnea monitor), per pair</td>
</tr>
<tr>
<td>A4557</td>
<td>Lead wires (e.g., apnea monitor), per pair</td>
</tr>
<tr>
<td>A4558</td>
<td>Conductive gel or paste, for use with electrical device (e.g., TENS, NMES), per oz.</td>
</tr>
<tr>
<td>A4595</td>
<td>Electrical stimulator supplies, 2 lead, per month, (e.g., TENS, NMES)</td>
</tr>
<tr>
<td>E0720</td>
<td>Transcutaneous electrical nerve stimulator (TENS) device, two leads, localized stimulation</td>
</tr>
<tr>
<td>E0730</td>
<td>Transcutaneous electrical nerve stimulator (TENS) device, four or more leads, for multiple nerve stimulation</td>
</tr>
</tbody>
</table>

Other HCPCS codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0283</td>
<td>Electrical stimulation (unattended), to one or more areas for indication(s) other than wound care, as part of a therapy plan of care</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F01.50 - F99</td>
<td>Mental disorders</td>
</tr>
<tr>
<td>G20</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>G21.4</td>
<td>Vascular parkinsonism</td>
</tr>
<tr>
<td>G25.81</td>
<td>Restless legs syndrome</td>
</tr>
<tr>
<td>G30.0 - G30.9</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>G43.001 - G43.919</td>
<td>Migraine</td>
</tr>
<tr>
<td>G44.001 - G44.89</td>
<td>Other headache syndromes</td>
</tr>
<tr>
<td>G47.00 - G47.9</td>
<td>Sleep disorders</td>
</tr>
<tr>
<td>G54.6 - G54.7</td>
<td>Phantom limb syndrome [associated with spinal cord injury]</td>
</tr>
<tr>
<td>I69.020, I69.120, I69.220, I69.320, I69.820, I69.920</td>
<td>Speech and language deficits following nontraumatic hemorrhage</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>I69.059, I69.159, I69.259, I69, 359, I69.859, I69.959</td>
<td>Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage</td>
</tr>
<tr>
<td>M54.10 - M54.18</td>
<td>Radiculopathy</td>
</tr>
<tr>
<td>M60.811 - M60.9</td>
<td>Myositis</td>
</tr>
<tr>
<td>M79.10 - M79.18</td>
<td>Myalgia</td>
</tr>
<tr>
<td>M79.2</td>
<td>Neuralgia and neuritis, unspecified</td>
</tr>
<tr>
<td>R40.0 - R40.4</td>
<td>Somnolence, stupor and coma</td>
</tr>
<tr>
<td>R51</td>
<td>Headache</td>
</tr>
<tr>
<td>S06.0x0+ - S06.9x9+</td>
<td>Intracranial injury [traumatic brain injury]</td>
</tr>
<tr>
<td>S12.000+ - S12.691+</td>
<td>Fracture of vertebral column [may be billed with codes for spinal cord injury]</td>
</tr>
<tr>
<td>S22.000+ - S22.089+</td>
<td></td>
</tr>
<tr>
<td>S32.000+ - S32.2xx+</td>
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</tr>
<tr>
<td>S14.101+ - S14.159+</td>
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</tr>
<tr>
<td>S24.101+ - S24.159+</td>
<td></td>
</tr>
<tr>
<td>S34.101+ - S34.139+</td>
<td></td>
</tr>
</tbody>
</table>

The above policy is based on the following references:
Transcranial Magnetic Stimulation:


40. Adelaide Health Technology Assessment (AHTA) on behalf of National Horizon Scanning Unit (HealthPACT and MSAC). Rapid transcranial magnetic stimulation for stroke rehabilitation; horizon scanning prioritizing summary - volume 15. Adelaide, SA: Adelaide Health Technology Assessment (AHTA) on behalf of National Horizon Scanning Unit (HealthPACT and MSAC); 2007.


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75. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry. 2010;71(7):873-884.


100. Slotema CW, Aleman A, Daskalakis ZJ, Sommer IE. Meta-analysis of repetitive transcranial magnetic stimulation in the treatment of auditory


113. Blue Cross and Blue Shield Association Medical Advisory Panel. Transcranial magnetic stimulation for depression. TEC Assessment Program. Chicago, IL: BCBSA; 2014;28(9).


142. Noda Y, Silverstein WK, Barr MS, et al. Neurobiological mechanisms of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal


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**Cranial Electrical Stimulation:**


Navigated Transcranial Magnetic Stimulation:


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: CPB 0469
Transcranial Magnetic Stimulation and Cranial Electrical Stimulation

There are no amendments for Medicaid.

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