

1. Executive Summary

1.1. Unmet Need in the Treatment of Depression

Major depression is common, recurrent, frequently chronic and a leading contributor to functional impairment and disability. It is estimated that 20% to 40% of patients do not benefit from or are unable to tolerate standard treatments¹. In addition, the large, NIMH-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study reported that 40.1% of patients who achieved remission after failing one adequate antidepressant course experienced relapse (mean time 4.1 months) over 12 months of follow-up². Thus, there is a need for more tolerable, effective, and durable options, especially in the setting of initial treatment resistance.

1.2. TMS Therapy as an Antidepressant

TMS Therapy is a therapeutic neuromodulation technique used for the treatment of patients with major depression. TMS is a noninvasive, non-systemic therapy that uses MRI-strength, pulsed, magnetic fields to induce an electric current in a localized region of the cerebral cortex. Sufficiently intense magnetic fields induce an electric current, which then causes depolarization of cortical neurons in a localized region of the brain immediately underneath the stimulation coil. Because the superficial cerebral cortex has extensive, trans-synaptic interconnections to deeper brain structures, this local depolarization leads to concurrent activation of brain regions distant from the site of stimulation. When applied to the left dorsolateral prefrontal cortex, TMS Therapy works in a targeted fashion directly on the neurocircuitry thought to control mood. Accumulating evidence suggests that repeated daily TMS sessions cause enduring changes in both brain function and clinical behavior³. Preclinical evidence has established that TMS exerts effects in animal models consistent with known effective antidepressant treatments⁴. When used as an antidepressant therapy, TMS produces a sustained clinical benefit without the systemic side effects typical with oral medications and has no adverse effects on cognition^{5,6}.

It is important to note that TMS is fundamentally different from the other established brain stimulation treatment, namely, electroconvulsive therapy (ECT). ECT involves the direct application of electric current to the scalp. With ECT, the electric current travels in diffuse paths through the brain, is always accompanied by the induction of a generalized motor convulsion, must be administered under general anesthesia, and produces significant post-treatment morbidity including long-lasting cognitive dysfunction in some patients.

1.3. TMS Therapy is a Proven, Safe and Effective Treatment for Depression

In October 2008, the US Food and Drug Administration cleared TMS Therapy, delivered by the NeuroStar TMS Therapy system manufactured by Neuronetics, Inc., “for the treatment of major depression in adult patients who failed to achieve satisfactory improvement from one prior antidepressant medication of adequate dose and duration in the current episode”. FDA clearance was based on a registration clinical trial program that included the largest multicenter, randomized, controlled trial of TMS in major depression^{5,7} as well as efficacy and durability open-label trials^{7,8}.

The clinical studies of TMS Therapy, using the NeuroStar TMS Therapy System, cumulatively encompass the largest database of clinical safety and efficacy data in for TMS in major depression assembled to date. This includes the initial registration studies conducted by Neuronetics in 2004-2006 and more recent, NIMH-sponsored, independent confirmatory studies that, in aggregate, firmly establish the use of high frequency stimulation of the left dorsolateral prefrontal cortex using the NeuroStar TMS Therapy System is an effective antidepressant treatment for patients who failed to benefit from initial antidepressant medication⁹. These studies used the same clinical protocol, in contrast to prior studies with older research TMS devices where a variety of protocols using different stimulation parameters and duration of treatments were used.

One of the most recently published meta-analyses, and among the largest to date¹⁰ examined data from 34 studies involving 1,383 patients. These authors reported an effect size of 0.55 (95% confidence interval 0.38 to 0.72) for the use of TMS in the treatment of depression, and concluded that, "...TMS deserves a place in the standard toolbox of psychiatric treatment methods, as it is effective for depression and has a mild side effect profile...".

The clinical research for NeuroStar TMS Therapy is the largest dataset for any TMS device worldwide. This data encompasses approximately 800 patients and nearly 15,000 TMS treatments and has been published in the peer-reviewed literature, including two multicenter, randomized, controlled clinical trials which include the NeuroStar TMS Therapy System registration trial^{5,7}, and the independent, NIMH-sponsored clinical trial⁹.

In addition to these two pivotal trials, the acute efficacy and safety of the NeuroStar TMS system has been studied in 2 open-label extension trials in patients who did not respond to the initial TMS or sham treatment^{8,11} and in 1 open-label, multisite, post-market study evaluating the efficacy in naturalistic use in patients across a unrestricted range of antidepressant treatment resistance^{12,13,14}. This recently published study which has evaluated the clinical outcomes of NeuroStar TMS Therapy in routine clinical practice has shown that real world outcomes with NeuroStar TMS are similar to those obtained in the open-label trials. The acute outcomes from this trial indicate that NeuroStar TMS under conditions of general clinical use is effective across a broad range of treatment resistance and illness morbidity. At the end of acute treatment, 62% of patients achieved symptomatic improvement while 41% reported complete remission.

Additionally, long-term outcomes following acute treatment with the NeuroStar TMS Therapy System have also been described in the peer-reviewed literature from the two multisite RCTs described above, extending for periods of 3 months¹⁵ and 6 months⁶ following the end of acute treatment, and for a period of 12 months following the end of acute treatment in the large, multisite naturalistic study noted above^{13,14}.

The safety and tolerability of currently available antidepressant treatments is a major concern in the clinical management of depression in patients who have failed to benefit from antidepressant treatment. From this perspective, the safety profile of NeuroStar TMS Therapy is particularly notable because of its high adherence rate, excellent tolerability and absence of systemic side effects. In controlled clinical studies of NeuroStar TMS, less than 5% of patients discontinued from acute treatment due to adverse events. Most frequently reported side effects associated with NeuroStar TMS

Therapy are pain or discomfort at or near the site of treatment which are usually experienced as mild to moderate and are transient, subsiding after the first week of treatment¹⁶.

1.4. TMS Therapy is Recognized by Expert Practice Guidelines and Evidence-Based Technology Reviews as a Safe and Proven Treatment for Major Depression

In clinical practice, NeuroStar TMS is an outpatient treatment that requires prescription by and use under the supervision of a physician. The treatment protocol is standardized as high frequency stimulation with the treatment coil positioned over the left dorsolateral prefrontal cortex. A standard treatment course for depression consists of 5 treatment sessions per week for 4 to 6 weeks, depending on patient response. Each NeuroStar TMS treatment is performed under continuous medical observation which results in high patient adherence.

TMS Therapy has gained general acceptance as a safe and proven treatment for major depression. The American Psychiatric Association's (APA) 2010 practice guidelines for the treatment of major depression state that, "*for patients whose symptoms have not responded adequately to medication, transcranial magnetic stimulation could also be considered*"¹⁷. The APA guidelines place TMS Therapy in the depression care pathway for patients whose symptoms have not been adequately treated by initial antidepressant medication. Two additional authoritative organizations have issued psychiatric treatment guidelines published in 2009 that reviewed the evidence of TMS efficacy and safety and made recommendations on its use for major depression. They are the Canadian Network for Mood and Anxiety Disorders¹⁸ and the World Federation of Societies for Biological Psychiatry¹⁹, both of which concluded there is now sufficient Level 1 evidence to support the use of TMS as an acute treatment for major depression.

Comprehensive technology reviews also provide support that TMS is an evidence-based treatment option for patients who have failed to benefit from initial acute phase treatment of major depression. In 2011, the federally-funded Effective Health Care Program of the Agency for Healthcare Research and Quality (AHRQ), published a Comparative Effectiveness Review (Number 33), entitled, "Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults"²⁰. Overall, the AHRQ Panel concluded that there is a substantial and well-replicated body of evidence from randomized, sham-controlled clinical trials that provide a "high strength of evidence" that TMS produces significantly greater decreases in depression severity, greater response rate and remission rate when compared to a sham treatment condition in the majority of peer-reviewed published clinical trials. Specifically, they noted that: "***...rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points relative to sham control, and this change meets the minimum threshold of the 3-point HAM-D difference that is considered clinically meaningful. Response rates were greater with rTMS than sham (also high strength of evidence); those receiving rTMS were more than three times as likely to achieve a depressive response as patients receiving sham procedure. Finally, rTMS was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving rTMS were more than 6 times as likely to achieve remission as those receiving the sham.***" The AHRQ Comparative Effectiveness report is particularly important because their findings represent a rigorously conducted, unbiased assessment

of the available scientific evidence. They stand in a unique and authoritative position as a statement on the favorable scientific and clinical conclusions that can be drawn from the peer-reviewed, published literature on the use of TMS in depression. Finally, they are consistent with the prevailing conclusions in the broader scientific literature regarding the safety and efficacy of the use of TMS in pharmacoresistant major depression.

In attempting to position the evidence for the various non-pharmacologic treatments in comparison to the outcomes expected for medication treatment as an alternative, the AHRQ report also summarizes the likelihood of patient benefit from the standard pharmacologic ‘next-step’ options. They report likelihood of achieving remission in patient with a routine pharmacologic “switch” to next best medication only averaged 22.3% (95% CI: 16.2% to 28.4%). With augmentation, the likelihood of achieving remission was similar, averaging 27.2% (95% CI: 20.4% to 34.0%). These numbers highlight the diminishing benefit with increasing levels of treatment resistance with standard pharmacologic options as compared with the clinician-rated remission rates observed in Neuronetics’ Outcomes Study 37.1% (95% CI: 31.9% to 42.7%).

The conclusions of the AHRQ report have been independently examined by the New England Comparative Effectiveness Public Advisory Council (CEPAC)²¹. CEPAC is an independent, 19-member organization composed of clinicians, patient and public health advocates, representatives of state public health programs and regional private payers from New England states. Their mission is to produce actionable information to aid regional policymakers in the medical policy decision-making process.

CEPAC is federally funded by the Agency for Healthcare Research and Quality (AHRQ) as part of its RAPID (Regional Adaptation for Payer Policy Decisions) initiative and is directed by the Institute for Clinical and Economic Review (ICER), a leading academic comparative effectiveness research group based at the Massachusetts General Hospital’s Institute for Technology Assessment. The CEPAC Panel rigorously reviewed the quality of the evidence provided in the original AHRQ report, and they extended the conclusions of that report by providing a detailed analysis of the anticipated direct impact on payor expenditures of providing TMS as a covered benefit.

Specifically, the CEPAC Panel arrived at the following conclusions:

- In a Panel vote on the fundamental question: “*For patients who have TRD[Treatment Resistant Depression], is the evidence adequate to demonstrate that rTMS provides a net health benefit equivalent or superior to usual care (i.e., general supportive psychotherapy with or without continued use of antidepressant medication)?*”, the CEPAC Panel voted **majority in support** of the conclusion that the scientific evidence on TMS demonstrates that TMS is clearly equivalent or superior to usual care.
- In a Panel vote on the separate question: “*For patients who have TRD, is the evidence adequate to demonstrate that rTMS provides a net health benefit equivalent or superior to ECT?*”, the CEPAC Panel again voted **majority in support** of the conclusion that the scientific evidence on TMS demonstrates that TMS provides a net health benefit that is equivalent or superior to the use of ECT.

- Finally, in a detailed economic analysis, the CEPAC Panel noted that using reasonable epidemiologically-based assumptions regarding the projected utilization of TMS in practice, *on a per member per month (PMPM) basis, the cost impact to payers of covering TMS ranges from \$0.21 - \$0.59, or a relatively modest 0.07 - 0.2% increase in plan costs.*

1.5. Current Reimbursement Status for TMS Therapy

In the United States, NeuroStar TMS Therapy is available in over 500 locations and in most states. NeuroStar TMS Therapy has been gaining recognition by payers for its clinical significance and it has been reimbursed as a medically-necessary treatment by over 115 payers. Patient access is granted through coverage policies and individual consideration which, in aggregate represents several million covered lives.

NeuroStar TMS Therapy is now in widespread clinical use across the country at nearly 500 centers, including institutions such as, Kaiser Permanente Hospital, Vanderbilt University, Ohio State University Harding Hospital, University of Texas Southwestern Medical Center, Stanford University, Mayo Clinic – Rochester MN, University of Michigan Depression Center of Excellence, Walter Reed Army Hospital, UCLA, the Harvard Medical System, Boston Medical Center, Johns Hopkins University, Cornell University, , Boston University, Brown University – Butler Hospital, UMDNJ- University of Medicine and Dentistry of New Jersey, Lindner Center of Hope, Medical University of South Carolina, Southern Illinois University, University of South Florida, University of Florida, Dent Neurologic Institute, Sheppard Pratt Center for Anxiety and Depression, and at freestanding hospitals and private physician’s offices.

TMS Therapy has received positive medical policy coverage nationwide. Medicare coverage policies (Local Coverage Determinations-LCD) have been issued in states such as Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, Alabama, Georgia, Florida, Puerto Rico, the Virgin Islands, Arkansas, Colorado, Louisiana, Mississippi, New Mexico, Oklahoma, Texas, North Carolina, South Carolina, Virginia, and West Virginia. Furthermore, large insurance entities have provided medical and behavioral coverage policies such as Anthem BCBS (including these states: BCBS Georgia, Connecticut, Empire BCBS New York, Ohio, Wisconsin, Indiana, Colorado, Anthem BC California, Missouri, New Hampshire, Nevada, Maine and Virginia), BCBS Federal Employee Program, Blue Shield of California, Independence BC, BCBS Massachusetts, BCBS Michigan, Blue Care Network of Michigan, BCBS Nebraska, Premera BC, BCBS Rhode Island, BCBS South Carolina, HealthNet/MHN, MVP Healthcare, Priority Health, Tufts Health Plan, VT Medicaid, and RI Medicaid only through Neighborhood Health Plan of RI. Additionally, behavioral health carve-out plans such as Magellan, Value Options, and OPTUM have proven treatment guidelines when determining medical necessity for TMS Therapy.

As described above, since 2009, additional literature has been published that collectively provides adequate scientific evidence to permit positive conclusions in technology reviews of TMS Therapy. Adequate, peer-reviewed, published scientific data now meets the general principles of evidence-based medicine.

Specifically, there is adequate evidence to:

- 1) Permit scientific conclusions about the efficacy and safety of TMS;
- 2) Show that TMS improves the health outcomes of patients, and;
- 3) Demonstrate that TMS is as least as beneficial, if not superior to, pharmacologic therapy in patients with depression that has not responded to prior antidepressant medication.

The CPT Editorial Research and Development committee of the AMA has granted TMS Therapy Category I CPT codes, effective January 1, 2011. The AMA has determined that TMS Therapy is consistent with current medical practice, is widely practiced throughout the country and has the support of the relevant medical societies.

Effective January 1, 2012, the following CPT I codes are to be used for reporting TMS Therapy medical services according to the three main phases of the treatment. These three codes are CPT 90867 (TMS treatment; initial, including cortical mapping, motor threshold determination, delivery and management) CPT 90868 (TMS treatment; subsequent delivery and management, per session) and CPT 90869 (TMS treatment; subsequent motor threshold re-determination with delivery and management).

1.6. Summary

In summary, support for the use of NeuroStar TMS Therapy as a proven, safe and effective treatment for patients with major depression can be found in the published scientific literature, by the supportive statements of expert consensus treatment guidelines, and in the increasing acceptance by practicing physicians and payers.

1.7. References

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