The New England Comparative Effectiveness Public Advisory Council

Coverage Policy Analysis:

Repetitive Transcranial Magnetic Stimulation (rTMS)

Completed by:

The Institute for Clinical and Economic Review
June 2012

This Coverage Policy Analysis is intended to provide a summary for payers of recent evidence and coverage policy development related to repetitive transcranial magnetic stimulation (rTMS) for the treatment of patients with treatment-resistant depression.

The origin of this material arises from the efforts of the New England Comparative Effectiveness Public Advisory Council (CEPAC). CEPAC is an initiative funded by the Agency for Healthcare Research and Quality (AHRQ) and led by our research team at the Institute for Clinical and Economic Review (ICER) at the Massachusetts General Hospital. CEPAC is an independent deliberative body composed of clinician and public representatives whose goal is to aid patients, physicians and policymakers in the interpretation and use of comparative effectiveness information to improve the quality and value of healthcare.

At its meeting in December, 2011, CEPAC reviewed the AHRQ evidence review on rTMS along with supplementary information on utilization, costs, and cost-effectiveness. CEPAC voted that the evidence was adequate to demonstrate that (rTMS), was as good as or better than usual care for patients with treatment-resistant depression. This Coverage Policy Analysis includes the following:

1. **CEPAC Voting Summary**: An overview of CEPAC’s votes on the comparative clinical effectiveness and value of TMS.

2. **New Regional Medicare Coverage Policy for rTMS**: In March 2012, citing in part the CEPAC report and votes, the Medicare Administrative Contractor for most of New England, NHIC, Corp, granted first-in-the-nation Medicare coverage for rTMS, reversing a non-coverage draft policy posted in November 2011. The language of the NHIC coverage policy is included.

3. **CEPAC Supplementary Report**: A review of the CEPAC meeting on treatment-resistant depression includes a breakdown of each vote on clinical effectiveness and comparative value, and describes some of the recommendations from CEPAC members concerning the evidence.

4. **Overview of the CEPAC initiative**: A brief one-page overview that describes the composition of CEPAC, the goal of the initiative and the impact it has had to date.

This information is being provided for informational purposes only. Neither CEPAC nor ICER makes specific recommendations concerning the coverage of rTMS or other options for treatment-resistant depression.

If you have any questions, please contact Sarah Jane Reed at 617-643-4568, sjreed@icer-review.org or Sarah Emond at 617-724-5497, semond@icer-review.org.
## CEPAC Voting Summary

**Nonpharmacologic Interventions for Treatment-Resistant Depression: rTMS**  
December 9, 2011

### rTMS vs. usual care

**Comparative clinical effectiveness:**
- A majority of CEPAC voted (10 to 5) that for patients with TRD, the evidence is 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).
  - CEPAC members split (5 to 5) on whether rTMS has a net health benefit that is superior or equivalent to usual care.

**Comparative value:**
- Based on the reimbursement levels provided in the final report, a majority of CEPAC voted that rTMS has reasonable value compared to usual care.
  - CEPAC votes:
    - High value: 0
    - Reasonable value: 6
    - Low value: 4

### rTMS vs. Electroconvulsive therapy (ECT)

**Comparative clinical effectiveness:**
- A majority of CEPAC voted (9 to 6) that for patients with TRD, the evidence is adequate to demonstrate that rTMS provides a net health benefit equivalent to ECT.

**Comparative value:**
- Based on the reimbursement levels provided in the final report, a majority of CEPAC voted that rTMS has low value compared to ECT.
  - CEPAC votes:
    - High value: 1
    - Reasonable value: 3
    - Low value: 5
Social value considerations for policymakers

When asked if there were considerations related to public health, equity, disparities in access or outcomes for specific patient populations, or other social values that should be considered in medical policies related to the use of rTMS, CEPAC voiced concern that with no third party reimbursement for rTMS, only patients who can afford to pay out-of-pocket can obtain treatment. Therefore, there may be concerns over equity in access to rTMS for certain populations.
New Regional Medicare Coverage Policy for rTMS
Local Coverage Determination (LCD) for Repetitive TRANSCRANIAL MAGNETIC STIMULATION (rTMS) (L32228)

Contractor Information

Contractor Name: NHIC, Corp.  
Contractor Number: 14101  
Contractor Type: MAC - Part A

LCD Information

Document Information

LCD ID Number: L32228

LCD Title: Repetitive TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

Primary Geographic Jurisdiction: Maine

Oversight Region: Region I

Original Determination Effective Date: For services performed on or after 03/17/2012

Revision Effective Date: For services performed on or after 03/17/2012

Original Determination Ending Date

Revision Ending Date

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CMS National Coverage Policy

CMS IOM Publication 100-1  
SSA §1816 & 1842 Contractor responsibility for determination of medically reasonable and necessary services, items  
1862 (a)(1)(D)&(E) Investigational or Experimental.

Indications and Limitations of Coverage and/or Medical Necessity
Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive, non-systemic treatment that uses Magnetic Resonance Imaging (MRI)-strength, pulsed, magnetic fields to induce an electric current in a localized region of the cerebral cortex. An electromagnetic coil is placed on the scalp that induces a focal current in the brain and temporary modulation of cerebral cortical function. Capacitor discharge provides electrical current in alternating on/off pulses. Depending on stimulation parameters, repetitive TMS to specific cortical regions can either decrease or increase the excitability of the targeted structures.

In 2008 the U.S. Food and Drug Administration (FDA) granted 510(k) marketing clearance as a de novo device (assessed as low risk, no predicate device) for NeuroStar® TMS to be utilized as a Class II rTMS device for the treatment of major depressive disorder in patients who had not responded to one adequate trial of antidepressant medication. A September 2011 AHRQ report “Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review” found that rTMS was beneficial relative to controls receiving a sham procedure for all three outcomes (severity of depressive symptoms, response rate, remission rate), with high strength of evidence for severity of depressive symptoms and response rate, and moderate strength of evidence for remission rate. Specifically, the AHRQ report cites that relative to sham control, rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points (a 3 point difference is considered clinically meaningful), a response rate three times greater, and a remission rates six times greater.

When used as an antidepressant therapy, rTMS may produce a clinical benefit without the systemic side effects typical with oral medications, has no adverse effects on cognition, and unlike electroconvulsant therapy does not induce amnesia or seizures. rTMS offers a well-tolerated, non-pharmacologic alternative that does not require attendant anesthesia services and can be administered in an outpatient setting for patients with DSM-IV defined Major Depressive Disorder who have failed to benefit from initial treatment of their depression. When effective, rTMS may prevent the need to utilize more complex pharmaceutical augmentation strategies (e.g., atypical antipsychotic medication), electroconvulsive therapy (ECT), and inpatient hospitalization at later stages of the illness.

**Covered Indications**

Left prefrontal rTMS is considered reasonable and necessary for patients diagnosed with severe Major Depression (single or recurrent episode) as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), who also have at least one of the following:

- Resistance to treatment with psychopharmacologic agents as evidenced by a lack of clinically significant response to four trials of such agents, in the current depressive episode, from at least two different agent classes. At least one of the treatment trials must have been administered at an adequate course of mono- or poly-drug therapy; or

- Inability to tolerate psychopharmacologic agents as evidenced by trials of four such agents with distinct side effects; or

- History of good response to rTMS in a previous episode; or

- If patient is currently receiving electro-convulsive therapy, rTMS may be considered reasonable and necessary as a less invasive treatment option.

**Cautionary Uses** – The benefits of rTMS use must be carefully considered against the risk of potential side effects in patients with any of the following:

- Seizure disorder or any history of seizure (except those induced by ECT or isolated febrile seizures in infancy without subsequent treatment or recurrence).

- The presence of vagus nerve stimulator leads in the carotid sheath.
The presence of an implanted medical device located <30 cm from the rTMS magnetic coil, including but not limited to pacemakers, implanted defibrillators, or vagus nerve stimulators.

**Coverage Limitations**

rTMS is considered not reasonable and necessary when used as a treatment modality for patients with any of the following:

- Presence of psychotic symptoms in current depressive episode.
- Chronic or acute psychotic disorder such as Schizophrenia, Schizophreniform Disorder, or Schizoaffective Disorder.
- rTMS should not be used in patients who have conductive, ferromagnetic or other magnetic-sensitive metals implanted in their head which are non-removable and within 30 cm of the rTMS magnetic coil. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coil, stents, and bullet fragments. Note: Dental amalgam fillings are not affected by the magnetic field and are acceptable for use with rTMS.

**Other Comments:**

Bill type codes only apply to providers who bill these services to the fiscal intermediary or Part A MAC. Bill type codes do not apply to physicians, other professionals and suppliers who bill these services to the carrier or Part B MAC.

Limitation of liability and refund requirements apply when denials are likely, whether based on medical necessity or other coverage reasons. The provider/supplier must notify the beneficiary in writing, prior to rendering the service, if the provider/supplier is aware that the test, item or procedure may not be covered by Medicare. The limitation of liability and refund requirements do not apply when the test, item or procedure is statutorily excluded, has no Medicare benefit category or is rendered for screening purposes.

**Coding Information**

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

013x Hospital Outpatient
023x Skilled Nursing - Outpatient
071x Clinic - Rural Health
073x Clinic - Freestanding
077x Clinic - Federally Qualified Health Center (FQHC)
085x Critical Access Hospital

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory; unless specified in the policy services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

0900 Behavioral Health Treatment/Services - General Classification

CPT/HCPCS Codes

GroupName

90867 THERAPEUTIC REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (TMS) TREATMENT; INITIAL, INCLUDING CORTICAL MAPPING, MOTOR THRESHOLD DETERMINATION, DELIVERY AND MANAGEMENT

90868 THERAPEUTIC REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (TMS) TREATMENT; SUBSEQUENT DELIVERY AND MANAGEMENT, PER SESSION

90869 THERAPEUTIC REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (TMS) TREATMENT; SUBSEQUENT MOTOR THRESHOLD RE-DETERMINATION WITH DELIVERY AND MANAGEMENT

ICD-9 Codes that Support Medical Necessity

296.23 MAJOR DEPRESSIVE AFFECTIVE DISORDER SINGLE EPISODE SEVERE DEGREE WITHOUT PSYCHOTIC BEHAVIOR
296.33 MAJOR DEPRESSIVE AFFECTIVE DISORDER RECURRENT EPISODE SEVERE DEGREE WITHOUT PSYCHOTIC BEHAVIOR

Diagnoses that Support Medical Necessity

ICD-9 Codes that DO NOT Support Medical Necessity

ICD-9 Codes that DO NOT Support Medical Necessity Asterisk Explanation

Diagnoses that DO NOT Support Medical Necessity

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General Information
Documentations Requirements
1. All documentation must be maintained in the patient’s medical record and available to the contractor upon request.
2. Every page of the record must be legible and include appropriate patient identification information (e.g., complete name, dates of service(s)). The record must include the physician or non-physician practitioner responsible for and providing the care of the patient.
3. The submitted medical record should support the use of the selected ICD-9-CM code(s). The submitted CPT/HCPCS code should describe the service performed.
4. The patient’s medical record must support the covered indications as detailed above.
5. The attending physician must monitor and document the patient’s clinical progress during treatment. The attending physician must use evidence-based validated depression monitoring scales like the Geriatric Depression Scale (GDS), the Personal Health Questionnaire Depression Scale (PHQ-9), the Beck Depression Scale (BDI) Hamilton Rating Scale for Depression (HAM-D), the Montgomery Asberg Depression Rating Scale (MADRS), the Quick Inventory of Depressive Symptomatology (QIDS) or the Inventory for Depressive Symptomatology Systems Review (IDS-SR) to monitor treatment response and the achievement of remission of symptoms.

Appendices

Utilization Guidelines
In accordance with CMS Ruling 95-1 (V), utilization of these services should be consistent with locally acceptable standards of practice.

rTMS is reasonable and necessary for up to 30 visits over a 7-week period followed by 6 taper treatments.

Repeat acute treatment for relapse of depressive symptoms is considered medically necessary if the patient responded to prior treatments, specifically > 50% improvement in a standard rating scale for depressive symptoms (e.g., GDS, PHQ-9, BDI, HAM-D, MADRS, QIDS or IDS-SR score). If patient meets the relapse criteria, up to 30 visits for the acute phase treatment followed by an additional 6 visits for tapering is considered reasonable and necessary.

The use of rTMS as a maintenance therapy is not supported by controlled clinical trial at this time and is therefore, considered not reasonable and necessary.

It is reasonable and necessary to report the treatment planning service (90867) once per course of treatment.

Sources of Information and Basis for Decision


Other Medicare contractors’ LCDs


NHIC Carrier Advisory Committee (CAC)
Advisory Committee Meeting Notes 10/24/2011
This policy does not reflect the sole opinion of the contractor or Contractor Medical Director. Although the final decision rests with the MAC contractor this policy was developed in cooperation with advisory groups which include representatives from various specialties, and adapted for the purpose of converting to MAC jurisdiction.

Start Date of Comment Period 10/24/2011

End Date of Comment Period 12/07/2011
Start Date of Notice Period 02/01/2012

Revision History Number R3

Revision History Explanation R3
03/17/2012
The >30 cm typographical error was corrected in the third bullet under "Cautionary Uses" in the Indications and Limitations of Coverage section to read <30cm

R2
03/17/2012
LCD is approved, effective for services rendered on or after 03/17/2012

R1
03/17/2012
Draft LCD was revised and finalized, effective for services rendered on or after 3/17/2012.

11/21/2011 - For the following CPT/HCPCS codes either the short description and/or the long description was changed. Depending on which description is used in this LCD, there may not be any change in how the code displays in the document:
90867 descriptor was changed in Group 1
90868 descriptor was changed in Group 1

Reason for Change Typographical Correction

Related Documents
This LCD has no Related Documents.

LCD Attachments
There are no attachments for this LCD.

All Versions
Updated on 01/27/2012 with effective dates 03/17/2012 - N/A
Updated on 01/19/2012 with effective dates 03/17/2012 - N/A
Read the LCD Disclaimer opens in new window
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CEPAC Supplementary Report
The New England Comparative Effectiveness Public Advisory Council

Repetitive Transcranial Magnetic Stimulation: Supplementary Data and Analyses to the Comparative Effectiveness Review of the Agency for Healthcare Research and Quality

FINAL MEETING REPORT – December 22, 2011
Edited to focus on rTMS only

Completed by:
The Institute for Clinical and Economic Review

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Introduction

To make informed healthcare decisions, patients, clinicians, and policymakers need to consider many different kinds of information. Rigorous evidence on the comparative clinical risks and benefits of alternative care options is always important; but along with this information, decision-makers must integrate other considerations. Patients and clinicians must weigh patients’ values and individual clinical needs. Payers and other policymakers must integrate information about current patterns of utilization, and the impact of any new policy on access, equity, and the overall functioning of systems of care. All decision-makers, at one level or another, must also consider the costs of care, and make judgments about how to gain the best value for every healthcare dollar.

The goal of this initiative is to provide a forum in which all these different strands of evidence, information, and public and private values can be discussed together, in a public and transparent process. Initially funded by a three-year grant from the federal Agency for Healthcare Research and Quality (AHRQ), and backed by a consortium of New England state policy makers, the mission of the New England Comparative Effectiveness Public Advisory Council (CEPAC) is to provide objective, independent guidance on how information from adapted AHRQ evidence reviews can best be used across New England to improve the quality and value of health care services. CEPAC is an independent body of 19 members, composed of clinicians and patient or public representatives from each New England state with skills in the interpretation and application of medical evidence in health care delivery. Representatives of state public health programs and of regional private payers are included as ex-officio members of CEPAC. The latest information on the project, including guidelines for submitting public comments, is available online: cepac.icer-review.org.

The Institute for Clinical and Economic Review (ICER) is managing CEPAC and is responsible for developing adaptations of AHRQ reviews for CEPAC consideration. ICER is an academic research group based at the Massachusetts General Hospital’s Institute for Technology Assessment. ICER’s mission is to lead innovation in comparative effectiveness research through methods that integrate evaluations of clinical benefit and economic value. By working collaboratively with patients, clinicians, manufacturers, insurers and other healthcare stakeholders, ICER develops tools to support patient decisions and medical policy that share the goals of empowering patients and improving the value of healthcare services. More information about ICER is available at www.icer-review.org.

ICER has produced this set of complementary analyses to provide CEPAC with information relevant to clinical and policy decision-makers in New England. This supplement is not meant to revisit the core scientific findings and conclusions of the AHRQ review on “Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults” but is intended to supplement those findings with: 1) updated information on the patient management options for treatment-resistant depression published since the AHRQ review; 2) regional and national data on prevalence, utilization, and existing clinical guidelines as well as payer coverage policies; and 3) the results of budgetary impact and cost-effectiveness analyses developed to support discussion of the comparative value of different management options. This report is part of an experiment in enhancing the use of evidence in practice and policy, and comments and suggestions to improve the work are welcome.
1. Background

1.1 The Condition

Major depressive disorder (MDD) is a common and debilitating condition; on an annual basis, it is estimated that nearly 14 million Americans will have at least one episode of MDD (Kessler, 2003). The impact of MDD is varied and complex; it has been found to negatively affect physical functioning, quality of life, productivity, and interpersonal relationships, often in an inter-related fashion (Klerman, 1992). MDD is also considered a major risk factor for Type 2 diabetes and coronary heart disease (von Knorring, 1996), and has been found to complicate the management and worsen the severity of many chronic conditions such as HIV/AIDS, Parkinson’s disease, and multiple types of cancer (Cassano, 2002).

For many patients, a cornerstone of treatment for MDD is the use of antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs), typically in combination with a form of psychotherapy. While medications are effective at reducing depressive symptoms in a significant number of patients, nonresponse to medications is common. The rate of nonresponse to one or more medication attempts has been estimated to range from 30-50% among patients presenting with a first episode of MDD (Cadieux, 1998; Thase, 1997). While definitions of so-called “treatment-resistant” depression (TRD) vary, this generally refers to patients with persistent depression after attempted management with two or more medications.

The heterogeneity of patient populations with MDD, the complexities involved in managing these patients, and the lack of a universally-effective treatment all combine to make MDD one of the most significant contributors to growing healthcare costs. The total burden of depression has been estimated at over $80 billion dollars annually in the US (Greenberg, 2003), nearly two-thirds of which is a consequence of lost work productivity due to depressive symptoms. The burden is most pronounced among patients with TRD. A recent study estimated total annual costs among employees with TRD to be nearly $15,000 per employee, which was more than twofold higher than costs among depressed employees without TRD (Greenberg, 2004). Evaluated costs included direct medical costs and indirect costs such as disability and absenteeism.

Given the failure of repeated treatment efforts to evoke a clinically-significant and lasting response for many patients, along with the costs and system impacts associated with managing these patients, there is significant interest on the part of patients, clinicians, policymakers, and other stakeholders in exploring different management options for TRD. This supplementary report builds on the conclusions of the AHRQ review by: describing recommendations and payer coverage policies for selected nonpharmacologic management options for TRD; identifying any new evidence on these options published since the AHRQ review; and finally, developing a simulation model to use findings from the AHRQ review to quantify the potential clinical and economic impact to the New England region of changes in the use of nonpharmacologic therapy for TRD.
1.2 Management Options for TRD

The management options of interest for this evaluation include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and two alternative forms of psychotherapy, cognitive-behavioral therapy (CBT), and interpersonal therapy (IPT). This edited report will focus on rTMS alone to the extent possible. The full report on all interventions is available at http://cepac.icer-review.org/wp-content/uploads/2011/04/Final-Report-TRD_FINAL2.pdf.

Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS involves the placement of a small wire coil on the scalp that conducts a varied and powerful electric current through it, creating a magnetic field through the tissues of the head (Wassermann, 1998). The current elicited by the electromagnetic coil is thought to stimulate nerve cells in the region of the brain involved in mood regulation and depression (Walter, 2001).

The procedure is performed in an office setting without anesthesia. Once the coil is placed, the electric current is turned on and off repeatedly at various locations on the head to find the optimal location (a process called “mapping”). When the current is on, a series of loud clicks or taps can be heard; the patient may be given earplugs to reduce the effects of these clicks. Once the optimal location is found, the physician will increase the magnetic dose until the patient’s fingers or hands twitch (known as the “motor threshold”) (Mayo Clinic, 2011). This is the dose that will be used for the session. Sessions are typically 40 minutes in length, after which the patient can usually resume normal activities. Treatment is typically administered daily (excluding weekends) for 2-6 weeks (Mayo Clinic, 2011).

Immediate side effects of rTMS include headache or scalp discomfort from the procedure, tingling, spasms, or twitches in the facial muscles, lightheadedness, and hearing discomfort from the procedure noise. Most of these effects are transient and improve throughout the course of treatment (Mayo Clinic, 2011). Rarely, rTMS has been reported to invoke seizures, and may also produce mania in patients with bipolar disorder; hearing loss from procedure noise also has been reported (Belmaker, 2003).

Other forms of electromagnetic therapy have begun to emerge. Recently, a novel coil, known as the “H-coil,” has been developed to enable stimulation of deeper brain regions (i.e., “deep TMS”) (Rosenberg, 2010). In addition, magnetic seizure therapy (MST) has also been developed, in which magnetic energy is used to induce therapeutic seizures. In contrast to ECT, these seizures are focal and limited to the prefrontal cortex in an attempt to limit any deleterious effects on cognition or memory (Kayser, 2011).

The FDA first approved rTMS in October 2008; it is indicated for the treatment of MDD in adults who have failed to achieve satisfactory improvement from at least one prior antidepressant medication used at or above the minimum effective dose and duration (U.S. FDA, 510(k) documentation, 2008).
2. Clinical Guidelines

2.1 Repetitive Transcranial Magnetic Stimulation (rTMS)

- American Psychiatric Association (2010)
  Data are insufficient to recommend rTMS as initial therapy in MDD. TMS may be an option for patients with inadequate response to pharmacotherapy.

  Due to lack of sufficient data regarding clinical efficacy, rTMS should be utilized in research studies only to provide further analysis of factors such as treatment duration and frequency and intensity of application. No major safety concerns have been identified with the use of TMS in severe depression.

- Institute for Clinical Systems Improvement (2011)
  While rTMS is recognized as an emerging therapeutic intervention in TRD, no specific recommendations are provided. Patients should be referred to specialists in psychiatry for evaluation.

3.1 Repetitive Transcranial Magnetic Stimulation

*National Payers*

- Centers for Medicare and Medicaid Services (CMS): Medicare has not made a national coverage decision on rTMS. No local coverage determinations have been made in New England, although local coverage decisions have been made in Mid-Atlantic States not to cover rTMS for depression, as it is considered investigational and not medically necessary.

- CIGNA, Aetna, and Wellpoint/Anthem do not cover rTMS for the treatment of depression because its value and effectiveness are not considered to be established.

*Regional Payers*

- BCBSMA, Harvard Pilgrim Health Care, Tufts Health Plan, and BCBSRI do not cover rTMS for depression because it is considered experimental, investigational, or unproven.

(NOTE: No published policies on transcranial magnetic stimulation were found for other regional payers, including ConnectiCare, BCBSVT, HealthNet, Neighborhood Health Plan of RI, and MVP Health Care.)
4. New Evidence Following AHRQ Review

4.1 Updated search

We conducted a systematic literature search of MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, and PsycInfo, utilizing the search criteria defined by the AHRQ review. The search timeframe spanned from January 1, 2010 to October 11, 2011. We identified 221 records after removal of duplicates (Figure 1). Any citations already included in the AHRQ review were removed. The remaining abstracts were screened using parameters designated by the AHRQ review (i.e., study type, patient population, treatment intervention and outcomes evaluated). Following initial screening, full-text review was performed on 54 retrieved articles. Forty-four of these were excluded for a variety of reasons, most commonly inappropriate study populations (e.g., more than 20% bipolar, patients without treatment-resistant disease) (Figure 1, p.9).

Ten articles were evaluated for new evidence (Appendix A). No randomized controlled trials (RCTs) were identified; most of the studies were small, single-center case series of relatively poor quality. For example, one series provided no details on the location, intensity, and conditions of ECT therapy (Oulis, 2011), while another did not specify the duration of follow-up (Sperling, 2011). Patient populations were heterogeneous with respect to the definition of treatment resistance, disease severity and duration of current depressive episode. Outcomes focused on examination of potential mechanisms of action of the different nonpharmacologic interventions, or assessment of predictors of response to the interventions. Two studies, described in more detail below, explored safety and quality of life (QoL) in TRD patients (Berlim, 2011, Oulis, 2011).

4.2 rTMS

In general, health-related quality of life (QoL) is under-evaluated in TRD patients. The AHRQ review identified six studies that assessed QoL, and only three of these evaluated patients undergoing rTMS. New observational data regarding QoL among patients receiving rTMS became available after publication of the AHRQ review. In a recent case series, 15 patients with treatment-resistant moderate to severe MDD, who maintained concurrent therapy with psychotropics, underwent high frequency-rTMS therapy over a four-week period (Berlim, 2011). Patients experienced significant improvement in their depressive symptoms, as measured with the HAM-D_{21} (p=0.035). Patients also experienced significant improvement in the World Health Organization’s Quality of Life Measure – Brief Version (WHOQOL BREF) overall score (p=0.017), as well as in physical and psychological domain scores. This study provides limited evidence regarding improved QoL in patients with TRD but due to the inherent biases within a case series, the results should be interpreted with care.
Figure 1. PRISMA flow diagram of included and excluded studies from updated literature search.

Titles and abstracts identified in MEDLINE, Cochrane, EMBASE and PsycInfo databases
N=273

Records after duplicates removed
N=221

Records screened
N=221

Records included in AHRQ review
N=88

Records excluded through abstract review
N=79

Full-text articles assessed for eligibility
N=54

Full-text articles excluded
N=44

Reasons for exclusion:
>20% bipolar patients, n=18
Mixed psychiatric diagnosis, n=5
Patients not uniformly refractory, n=20
No specific outcome measures described, n=1

Articles included in ICER qualitative synthesis
N=10
5. Analysis of Comparative Value

5.1 Methods

An economic model was developed to evaluate the comparative value of nonpharmacologic therapies for use in patients with TRD. The comparative value of these strategies was considered in two ways: the budget impact to public and/or private payers of changing coverage policy (and the associated distribution of management options utilized) and the cost-effectiveness of a given management option vs. a comparator option. Budget impact was analyzed on a population basis and considered the impact of changes in coverage, resource utilization, and cost among Medicaid beneficiaries and members of the three largest private payers in each New England state. Cost-effectiveness was evaluated in a hypothetical cohort of 1,000 patients and considered the outcomes and costs associated with each modeled treatment “pathway”.

Management Options

Only nonpharmacologic interventions demonstrating sufficient evidence of effectiveness and safety in the AHRQ evaluation were considered in the economic analyses (see Table 1 on the following page). The budget impact analyses considered scenarios in which varying percentages of use of ECT and rTMS are assumed in a population of patients with TRD.

Analyses of cost-effectiveness were limited to a comparison of rTMS to usual care, as this was the only comparison in the AHRQ review demonstrating sufficient evidence of a difference in net clinical benefit (Gaynes, 2011).

Key treatment parameter estimates may be found in Table 1 on the following page. Estimates for treatment response and remission were obtained from meta-analyses conducted in the AHRQ review. Estimates of response and remission for ECT and rTMS were obtained directly from head-to-head data reported in Table 11 of the AHRQ review (Gaynes, 2011). These rates are assumed equal for ECT and rTMS given the conclusions drawn in the comparative effectiveness review that there are no significant differences in changes in depressive severity, response, or remission between these two options. Estimates of the risk of relapse were also assumed to be equal based on the findings reported in Table 35 of the review (Gaynes, 2011). The corresponding usual care inputs were derived by applying the inverse of the meta-analyzed relative risk of these outcomes for rTMS vs. usual care (Figures 13 and 14, and Table 37 for response, remission, and relapse in the AHRQ review). As there were no data differentiating management alternatives in terms of relapse rates, a uniform monthly risk was assumed across all options.
Table 1. Treatment parameters.

<table>
<thead>
<tr>
<th>Unit Item</th>
<th>Usual Care</th>
<th>ECT</th>
<th>rTMS</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response* to treatment</td>
<td>27.1%</td>
<td>59.1%</td>
<td>59.1%</td>
<td>Course of therapy</td>
</tr>
<tr>
<td>Remission† on treatment</td>
<td>24.9%</td>
<td>59.1%</td>
<td>59.1%</td>
<td>Course of therapy</td>
</tr>
</tbody>
</table>

* 20-50% change on depression scale
† HAM-D17 < 8, HAM-D21 < 10, or MADRS < 8

Demographic characteristics of patients with TRD, as well as estimates of resource use and payment under conditions of typical practice, were obtained from regional benchmark information provided by the proprietary LifeLink™ Health Plan Claims Database (IMS Health, Danbury, CT), which is comprised of 79.4 million privately-insured individuals from 79 health plans nationwide and includes 6.7 billion medical and pharmacy claims generated from 2001 to the present. The population was restricted to patients aged 20-64 years, who were located in the Northeast U.S. Census region, and had one or more claims with a diagnosis of depression in 2008. Utilization and cost data were generated for calendar year 2009.

**Clinical and Economic Model**

The model framework considers the outcomes of a population consisting of 30% men between the ages 20 and 64 years with a mean age of 45 years across the entire population. The age range was selected because (a) the AHRQ review focused on adults only; and (b) the population of most interest for decision-makers in each New England state was felt to include Medicaid and privately-insured patients only. Medicare patients were therefore excluded from consideration.

Population characteristics were consistent with those of the IMS database as described above. All patients were assumed to carry a diagnosis TRD consistent with that used in the AHRQ report (i.e., depression that is non-responsive to two or more trials of drug therapy). All costs and payments are reported in 2010 US dollars unless otherwise specified.

**Key Model Assumptions about TRD Management Options (Budget Impact and Cost-Effectiveness Analyses)**

- The primary measure of clinical impact is the proportion of treated patients with a “positive treatment response.” Definitions of response varied by study, but generally are based on improvement of 20-50% on a standardized depression scale such as the Hamilton Rating Scale for Depression (HAM-D).
- Remission rates were applied in accordance with the definitions used in the AHRQ review, in which patients who reached a minimum threshold score (i.e., HAM-D17 < 8, HAM-D21 < 10, or MADRS < 8) were felt to have achieved full remission.
- All patients under all treatment scenarios were assumed to continue with usual care (e.g., therapy visits, prescription medications) regardless of the outcome of nonpharmacologic intervention.
Rates of effectiveness and harm were assumed to be identical for ECT and rTMS, based on findings from head-to-head trials reported in the AHRQ review.

rTMS was assumed to be more effective than usual care, consistent with the AHRQ review’s meta-analysis of the rTMS vs. sham trials.

Based on the reported range of course of therapy reported in the AHRQ review, ECT was assumed to involve twice-weekly sessions of 3-4 hours each over a total of four weeks, while rTMS was assumed to involve daily sessions (five days per week) of 40 minutes each over a total of four weeks. Total estimated cost for each course of therapy was assumed to be approximately $3,500 and $4,400 for ECT and rTMS respectively, including the costs of planning visits, treatment delivery, and anesthesia (ECT only).

Key Model Assumptions about TRD Management Options (Cost-Effectiveness Analysis Only)

- The patient group with a positive treatment response to nonpharmacologic intervention is assumed to benefit from fewer emergency department (ED) and inpatient admissions.
- Changes in resource use associated with a positive treatment response or relapse are applied over the course of 6 months, corresponding to the model cycle length.
- Risk of relapse is applied in the second 6-month cycle and thereafter.
- For patients that suffer a relapse, it is assumed that resource use for ED and inpatient admissions returns to the higher frequency associated with TRD.
- Among the group of patients who relapse, 50% of those previously on ECT or rTMS are assumed to retry the same nonpharmacologic strategy following relapse, whereas 100% of all patients who relapse on usual care are assumed to retry usual care.
- In calculating the impact on lost wages in the cost-effectiveness analysis, the distribution of employment status was assumed to be: employed full-time (71%), part-time (16%), unemployed (8%) or receiving disability (5%).

Key Assumptions about TRD

Major assumptions regarding the course of TRD and its treatment can be found below; detailed input parameter estimates can be found in Table 2 on the following page.

Population
The age and gender distribution was assumed from the data provided by IMS Health. Accordingly, 70% of TRD patients aged 20-64 years were assumed to be female, and 60% were assumed to be aged 45-64 years.

Prevalence
The prevalence of TRD in the private payer population was estimated to be 2.0% based on a published epidemiologic estimate (Ivanova, 2010) for males and females irrespective of age. The corresponding prevalence among Medicaid recipients was derived by applying a relative risk of 1.69 from a study comparing depression prevalence by socioeconomic status (Lorant, 2003) to the prevalence of TRD in the private payer population, resulting in an estimated prevalence of 3.4%.
Table 2. General model input parameters

<table>
<thead>
<tr>
<th>Unit Item</th>
<th>Input</th>
<th>Unit</th>
<th>Frequency</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male patients</td>
<td>30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age: Male/Female</td>
<td>45.5/45.4</td>
<td>Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Employment Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-Time</td>
<td>71.10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part-Time</td>
<td>15.60%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>8.10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td>5.10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Payment Items – Private</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient Visits</td>
<td>$584</td>
<td>per visit</td>
<td>2.4</td>
<td>per year</td>
</tr>
<tr>
<td>Office Visits</td>
<td>$115</td>
<td>per visit</td>
<td>13.7</td>
<td>per year</td>
</tr>
<tr>
<td>Emergency Department</td>
<td>$1,089</td>
<td>per visit</td>
<td>0.3</td>
<td>per year</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$60</td>
<td>per script</td>
<td>31.2</td>
<td>per year</td>
</tr>
<tr>
<td>ECT</td>
<td>$433.58</td>
<td>per session</td>
<td>8</td>
<td>per course of therapy</td>
</tr>
<tr>
<td>rTMS planning</td>
<td>$246</td>
<td>per session</td>
<td>1</td>
<td>per course of therapy</td>
</tr>
<tr>
<td>rTMS delivery</td>
<td>$206</td>
<td>per session</td>
<td>20</td>
<td>per course of therapy</td>
</tr>
<tr>
<td>Inpatient Facility Admission</td>
<td>$11,296</td>
<td>per admission</td>
<td>0.1</td>
<td>admissions per year</td>
</tr>
<tr>
<td>Inpatient Professional Visit</td>
<td>$330</td>
<td>per visit</td>
<td>4.7</td>
<td>visits per admission</td>
</tr>
<tr>
<td><strong>Indirect Cost Items</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional employment wage</td>
<td>$23.57</td>
<td>per hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional disability benefit</td>
<td>$962.58</td>
<td>per month</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reason for Productivity Loss</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General depression overall</td>
<td>51.2</td>
<td>Days lost/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medically related</td>
<td>13.5</td>
<td>Days lost/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td>37.7</td>
<td>Days lost/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual care</td>
<td>0</td>
<td>Additional days lost/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rTMS treatment</td>
<td>11</td>
<td>Days lost/course of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Utility Items</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline TRD - Male</td>
<td>0.708</td>
<td>Annual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline TRD – Female</td>
<td>0.708</td>
<td>Annual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>Annual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change due to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aging</td>
<td>-0.00251</td>
<td>Annual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECT</td>
<td>0</td>
<td>Per course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rTMS</td>
<td>0</td>
<td>Per course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual care</td>
<td>0</td>
<td>Per course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>0.0625</td>
<td>Per response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>0.125</td>
<td>Per remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>-0.0625</td>
<td>Per relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious Adverse Event</td>
<td>-0.1</td>
<td>Per event</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mortality
Overall age and gender-specific mortality was obtained from the 2007 U.S. life tables (Arias, 2011). Hazard ratios from a published study on the association between major depression and all-cause mortality (Zheng, 1997) were applied to these data to estimate the increased risk of death among men and women with TRD. Adjusted hazard ratios of 3.1 for males and 1.7 for females were applied to the gender-specific risks in the general population. The resulting risk of death for patients with TRD was approximately 3.3% per year for males and 1.8% per year for females.

Loss of Productivity and Wages
Lost wages were estimated using data from the 2009 U.S. Census data for residents of the Northeast U.S. (U.S. Census Bureau, 2009). The proportion of patients receiving disability benefits (5.1%) and average benefit paid ($963/month) was derived from regional New England data (Office of Retirement and Disability Policy, 2009). Average hourly wages ($23.57) were obtained from the Bureau of Labor Statistics (Bureau of Labor Statistics, 2010) and used to derive a mean estimate for New England. Days of work lost due to disability or medically-related issues was obtained from a published study (Ivanova, 2010). Work loss due to the time required for ECT and rTMS treatment was assumed based on the typical course of therapy reported in the AHRQ review. Specifically, rTMS was assumed to involve four hours of work loss for each session.

Utility Estimates
Weights to adjust for changes in quality of life were obtained from the literature. The utility for men and women suffering from TRD was set to 0.708 based on data from an epidemiologic study (Sullivan, 2006). Adjustments were made to account for the general impact of aging, remission, and relapse.

Payments and Resource Utilization
The average paid amount for each resource use item was derived from the IMS LifeLink database as previously-described, and was used as the model input to represent the direct cost to a private payer (Table 3 on the following page). Medicaid payments were assumed to be 60% of those received by private payers. Because patients with TRD were assumed to have more severe symptoms, routine resource use for patients with general depression was adjusted using a literature-based, resource-specific factor (Ivanova, 2010) to estimate likely resource consumption among patients with TRD. Payment estimates from prior years were inflated to 2010 using the overall medical inflation component of the consumer price index for the Northeast U.S. (Bureau of Labor Statistics, 2010). All resulting payment and frequency inputs are presented in page 13.

Budget Impact
The budget impact analysis estimates the regional impact of introducing coverage for rTMS in New England as determined by the number of insured adult lives covered under Medicaid and by the three largest private payers in each of the six New England states (Table 3 on the following page). The total number of patients with TRD is calculated using separate prevalence estimates for the private payer and Medicaid populations. This may be further specified by population age category and gender. Use of ECT and rTMS in the TRD population before and after introduction of a new coverage decision is specified as the percentage of patients treated with each option.
Table 3. Estimated number of enrollees in budget impact analyses, by state and payer type.

<table>
<thead>
<tr>
<th>State</th>
<th>Medicaid(*)</th>
<th>Private Payer‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>163,800</td>
<td>1,383,791</td>
</tr>
<tr>
<td>ME</td>
<td>135,700</td>
<td>807,396</td>
</tr>
<tr>
<td>MA</td>
<td>690,900</td>
<td>2,396,386</td>
</tr>
<tr>
<td>NH</td>
<td>35,500</td>
<td>341,054</td>
</tr>
<tr>
<td>RI</td>
<td>78,100</td>
<td>1,246,212</td>
</tr>
<tr>
<td>VT</td>
<td>63,700</td>
<td>270,755</td>
</tr>
</tbody>
</table>

† Kaiser Family Foundation, State health facts. Age Distribution of Medicaid Enrollees, FY 2007
‡ U.S. News & World Report LP; http://health.usnews.com/health-plans

The payments associated with ECT and rTMS treatment, routine care for depression, adverse events related to treatment, and resource use as a result of relapse are estimated at baseline and over multiple scenarios evaluating increased use of rTMS. Findings are reported on an annual basis. In addition, 50% of patients who relapse are assumed to retry the same strategy again within the year.

Over the one-year time horizon, the model estimates the total number of patients with TRD, the proportion treated using ECT or rTMS, the subset of treated patients who would be expected to have a positive response, and the corresponding resources consumed and associated payments. Payments are reported as total payments per patient with TRD, annual plan payments for all patients with TRD, annual payments for all services for all members, and payments per member per month (PMPM) for all members.

At baseline, 20% of TRD patients are assumed to be receiving ECT. In the first modeled scenario (Scenario 1), one-half of the patients receiving ECT are assumed to switch to rTMS. In the second scenario, (Scenario 2), the percentage of patients receiving ECT is assumed to remain constant at 20%, and an additional 10% of TRD patients are assumed to undergo rTMS treatment rather than continue with usual care for TRD. Each scenario is considered separately for Medicaid beneficiaries, privately-insured patients, and a combination of the two groups over the entire region. In addition, state-specific analyses are presented in Appendix B for the combined Medicaid/private population.

**Cost-Effectiveness**

The cost-effectiveness analysis considers the experience of a cohort of 1,000 hypothetical patients diagnosed with TRD who are treated with either rTMS or usual care over the course of five years. During this time, patients may respond to treatment and are at risk for early treatment withdrawal, adverse events, hospitalization, relapse among those in remission, death from any cause and TRD-related death (i.e., suicide and other excess mortality from depression) in six-month cycles. The payments associated with these outcomes and treatment accumulate over five years, yielding the estimated total direct medical cost of using rTMS vs. usual care in patients with TRD. In addition, the indirect costs associated with lost productivity due to treatment and TRD in general are taken into account providing a broader perspective. Lost wages and disability payments are estimated for patients and summed over the period of analysis. The present value of all costs accrued in the future is estimated using an annual discount rate of 3.5%, consistent with typical practice in long-term economic evaluations.
Total time alive, or life years, is estimated by summing the total number of patients alive at each time point. This outcome is weighted to estimate the total quality-adjusted life years (QALYs), which accounts for changes in quality of life determined by the experiences of the patient group and the duration over which they occur. Specifically, the amounts of time patients are in remission, relapsed, in hospital, and dead are multiplied by the “weight” associated with each of these states and summed over the population.

Effectiveness outcomes are presented for each strategy in terms of the numbers of patients with a positive treatment response or remission, relapse, inpatient stay, or death; total life years and QALYs are also reported for each cohort. Costs associated with each of these categories are presented as the total cost and by component for each strategy. Cost-effectiveness results are presented as incremental cost-effectiveness ratios (ICERs) for rTMS relative to usual care. Measures of interest included cost per life-year gained (LYG), cost per QALY gained, and cost per additional positive treatment response.

5.2 Results

*Estimated Region-wide Budget Impact – All Payers*

The distribution of patients represented by Medicaid and private payers in this analysis is shown by New England state in Table 4 below along with the estimated prevalence and resulting number of patients with TRD.

Table 4. Estimated TRD population, by payer type.

<table>
<thead>
<tr>
<th>New England State Distribution</th>
<th>Medicaid</th>
<th>Private Payer</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>CT</td>
<td>163,800</td>
<td>11%</td>
<td>1,383,791</td>
</tr>
<tr>
<td>ME</td>
<td>135,700</td>
<td>14%</td>
<td>807,396</td>
</tr>
<tr>
<td>MA</td>
<td>690,900</td>
<td>22%</td>
<td>2,396,386</td>
</tr>
<tr>
<td>NH</td>
<td>35,500</td>
<td>9%</td>
<td>341,054</td>
</tr>
<tr>
<td>RI</td>
<td>78,100</td>
<td>6%</td>
<td>1,246,212</td>
</tr>
<tr>
<td>VT</td>
<td>63,700</td>
<td>19%</td>
<td>270,755</td>
</tr>
</tbody>
</table>

Proportion of patients by payer (%) 15% 85%

*Covered Populations*:

| Total membership (n) | 1,167,700 | 6,445,594 | 7,613,294 |
| Prevalence of TRD    | 3.4%      | 2.0%      | 2.2%      |
| Patients with TRD (n)| 39,468    | 128,912   | 168,380   |

*Note that uninsured patients are not represented in this analysis as there is no direct impact to a third party payer.*

Shifting 10% of patients from ECT to rTMS in Scenario 1 resulted in no change in the number of patients having a positive treatment response relative to baseline (see Table 5 on the following page) due to the underlying assumption of equivalent efficacy for ECT and rTMS. In Scenario 2, in which 10% of the population receiving usual care at baseline was assumed to begin rTMS, an additional 3.2% of patients overall are estimated to have a positive treatment response.
Table 5. Estimated clinical impact of ECT and rTMS in an insured population.

<table>
<thead>
<tr>
<th>Summary of Covered Population</th>
<th>Baseline</th>
<th>Scenario 1* †</th>
<th>Net Change vs. Baseline</th>
<th>Scenario 2* ‡</th>
<th>Net Change vs. Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total membership (n)</td>
<td>7,613,294</td>
<td>7,613,294</td>
<td></td>
<td>7,613,294</td>
<td></td>
</tr>
<tr>
<td>Patients with TRD (n)</td>
<td>168,380</td>
<td>168,380</td>
<td></td>
<td>168,380</td>
<td></td>
</tr>
<tr>
<td>Patients with TRD receiving ECT and/or TMS (n)</td>
<td>33,676</td>
<td>33,676</td>
<td>50,514</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>As a proportion of all members</td>
<td>20.0%</td>
<td>20.0%</td>
<td>30.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes &amp; Resource Use</td>
<td>Positive Treatment Response (n)</td>
<td>56,421</td>
<td>56,421</td>
<td>0</td>
<td>61,807</td>
</tr>
<tr>
<td>Positive Treatment Response (%)</td>
<td>33.5%</td>
<td>33.5%</td>
<td>36.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

The uptake of rTMS in Scenarios 1 and 2 resulted in a net economic impact of 1.1% and 3.1%, respectively, relative to baseline due to the increased cost of rTMS therapy, corresponding to an increase in total payments of approximately $19 million in Scenario 1 and $53.5 million in Scenario 2 across the region (see Table 6 on the following page). Total cost per patient treated with nonpharmacologic therapy ranged from $10,101 – $10,419 annually, depending on the uptake of rTMS. Annual payments are estimated to increase $93 - $318 per patient given a 10% uptake of rTMS, depending on the scenario (Table 6 on the following page). On an overall basis, the PMPM was estimated to increase by $0.21 and $0.59 for scenarios 1 and 2 respectively.
Table 6. Estimated economic impact of ECT and rTMS use in an insured population.

<table>
<thead>
<tr>
<th>Estimated Region-wide Budget Impact</th>
<th>Medicaid Only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table 7</strong> below shows the absolute number of patients represented in the Medicaid-only analysis. Uptake of rTMS among patients receiving Medicaid resulted in a 2.6-4.6% increase in payments for all patients with TRD. Total cost per patient treated with nonpharmacologic therapy ranged from $6,688 – $6,995 annually, depending on the uptake of rTMS (Table 8 on the following page).</td>
<td></td>
</tr>
</tbody>
</table>

### Table 7. Estimated clinical impact of ECT and rTMS use in the Medicaid population.

<table>
<thead>
<tr>
<th>Summary of Covered Population</th>
<th>Baseline</th>
<th>Scenario 1*'†</th>
<th>Net Change vs. Baseline</th>
<th>Scenario 2*'‡</th>
<th>Net Change vs. Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total membership (n)</td>
<td>1,167,700</td>
<td>1,167,700</td>
<td>1,167,700</td>
<td>1,167,700</td>
<td>1,167,700</td>
</tr>
<tr>
<td>Patients with TRD (n)</td>
<td>39,468</td>
<td>39,468</td>
<td>39,468</td>
<td>39,468</td>
<td>39,468</td>
</tr>
<tr>
<td>Patients with TRD receiving ECT and/or TMS (n)</td>
<td>7,893</td>
<td>7,893</td>
<td>11,840</td>
<td>0.7%</td>
<td>11,840</td>
</tr>
<tr>
<td>As a proportion of all members</td>
<td>0.7%</td>
<td>0.7%</td>
<td>1.0%</td>
<td>20.0%</td>
<td>20.0%</td>
</tr>
<tr>
<td>As a proportion of patients with TRD</td>
<td>20.0%</td>
<td>20.0%</td>
<td>30.0%</td>
<td>30.0%</td>
<td>30.0%</td>
</tr>
<tr>
<td>Outcomes &amp; Resource Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive Treatment Response (n)</td>
<td>13,225</td>
<td>13,225</td>
<td>0</td>
<td>14,488</td>
<td>1,263</td>
</tr>
<tr>
<td>Positive Treatment Response (%)</td>
<td>33.5%</td>
<td>33.5%</td>
<td>36.7%</td>
<td>36.7%</td>
<td>36.7%</td>
</tr>
</tbody>
</table>

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.
Table 8. Estimated economic impact of ECT and rTMS use in the Medicaid population.

<table>
<thead>
<tr>
<th></th>
<th>Scenario 1</th>
<th></th>
<th>Scenario 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Payments</td>
<td>Net Change</td>
<td>Baseline</td>
</tr>
<tr>
<td>Payments per patient with TRD (n=39,468)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECT and/or TMS</td>
<td>$442</td>
<td>$614</td>
<td>$172</td>
<td>$835</td>
</tr>
<tr>
<td>Outpatient Management &amp; ER</td>
<td>$5,142</td>
<td>$5,142</td>
<td>$0</td>
<td>$5,110</td>
</tr>
<tr>
<td>Inpatient admissions</td>
<td>$1,103</td>
<td>$1,103</td>
<td>$0</td>
<td>$1,050</td>
</tr>
<tr>
<td>Total per patient</td>
<td>$6,688</td>
<td>$6,860</td>
<td>$172</td>
<td>$6,995</td>
</tr>
<tr>
<td>Annual payments for all patients with TRD</td>
<td>$263,949,131</td>
<td>$270,732,493</td>
<td>$6,783,361</td>
<td>$276,085,572</td>
</tr>
<tr>
<td>Annual payments for all services (all patients)</td>
<td>$2,648,406,478</td>
<td>$2,655,189,839</td>
<td>$6,783,361</td>
<td>$2,660,542,918</td>
</tr>
<tr>
<td>Payment per member per month - overall (PMPMo)</td>
<td>$189.00</td>
<td>$189.49</td>
<td>$0.48</td>
<td>$189.87</td>
</tr>
</tbody>
</table>

2.6% 4.6%

Plan payments for Covered Population (n=1,167,700)

|                                      | Scenario 1 |         | Scenario 2 |         |
|                                      | Baseline   | Payments| Net Change | Baseline| Payments|
| Annual payments for all services (all patients) | $2,648,406,478 | $2,655,189,839 | $6,783,361 | $2,660,542,918 | $12,136,441 |
| Payment per member per month - overall (PMPMo) | $189.00 | $189.49 | $0.48      | $189.87 | $0.87   |

*Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
†Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.
‡TMS and ECT are assumed to have equivalent efficacy, therefore, no cost offset is considered due to improved response.

Estimated Region-wide Budget Impact – Private Payer

On a percentage basis, the increases in payments for private payers managing treatment of patients with TRD (Table 9 on the following page) were predicted to be incrementally less than predicted for Medicaid (ranging from 0.9% - 2.9% in total) given the assumed lower prevalence of TRD among private payer populations (Table 10 on the following page). Total cost per patient treated with nonpharmacologic therapy ranged from $11,146 – $11,467 annually, depending on the uptake of rTMS.
Table 9. Estimated clinical impact of ECT and rTMS use in a private payer population.

<table>
<thead>
<tr>
<th>Summary of Covered Population</th>
<th>Baseline</th>
<th>Scenario 1*†</th>
<th>Net Change vs. Baseline</th>
<th>Scenario 2*‡</th>
<th>Net Change vs. Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total membership (n)</td>
<td>6,445,594</td>
<td>6,445,594</td>
<td>6,445,594</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with TRD (n)</td>
<td>128,912</td>
<td>128,912</td>
<td>128,912</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with TRD receiving ECT and/or TMS (n)</td>
<td>25,782</td>
<td>25,782</td>
<td>38,674</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As a proportion of all members</td>
<td>0.4%</td>
<td>0.4%</td>
<td>0.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As a proportion of patients with TRD</td>
<td>20.0%</td>
<td>20.0%</td>
<td>30.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcomes & Resource Use

| Positive Treatment Response (n) | 43,196 | 43,196 | 0 | 47,320 | 4,124 |
| Positive Treatment Response (%) | 33.5% | 33.5% | 36.7% | | |

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Table 10. Estimated economic impact of ECT and rTMS use in a private payer population.

<table>
<thead>
<tr>
<th>Payments per patient with TRD (n=128,912)</th>
<th>Scenario 1*†</th>
<th>Scenario 2*‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECT and/or TMS</td>
<td>Baseline</td>
<td>Payments</td>
</tr>
<tr>
<td>$737</td>
<td>$832</td>
<td>$95</td>
</tr>
<tr>
<td>$8,571</td>
<td>$8,571</td>
<td>0</td>
</tr>
<tr>
<td>$1,839</td>
<td>$1,839</td>
<td>0</td>
</tr>
<tr>
<td>$11,146</td>
<td>$11,241</td>
<td>$95</td>
</tr>
<tr>
<td>Annual payments for all patients with TRD</td>
<td>$1,436,858,324</td>
<td>$1,449,147,639</td>
</tr>
<tr>
<td>Annual payments for all services (all patients)</td>
<td>$24,364,923,787</td>
<td>$24,377,213,101</td>
</tr>
<tr>
<td>Payment per member per month - overall (PMPMo)</td>
<td>$315.01</td>
<td>$315.17</td>
</tr>
</tbody>
</table>

*TMS and ECT are assumed to have equivalent efficacy, therefore, no cost offset is considered due to improved response.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Cost-Effectiveness of TRD Management Strategies

rTMS is associated with a 13.6% increase in the number of positive treatment responses over usual care over five years; in addition, the number of full remissions was 15.9% higher under the rTMS strategy (Table 11 on page 22). Note that a reference copy of Table 2 (model input parameters) follows this table (page 23) to assist in the interpretation of Table 11.
The cumulative discounted cost associated with managing patients with TRD treated with rTMS is estimated to be $35,550 per patient over five years compared with $31,296 for patients under usual care. This is driven entirely by treatment costs and represents a 13.6% increase in payments associated with managing TRD. When indirect, non-medical costs are considered, these estimates increase to $70,205 and $76,530 for rTMS and usual care, respectively.

A cost per life-year gained could not be estimated, as survival is assumed to be the same for each strategy. Quality adjusted life years differed by a factor of 0.5% favoring rTMS and yielding a cost/QALY gained of $216,468 per patient, based on discounted direct medical costs (Table 11 on the following page). Improvements in treatment response with rTMS resulted in a cost per additional treatment response gained of $11,803 for rTMS.

When indirect costs were taken into consideration, the cost per QALY gained increased to $321,880 and the cost per additional treatment response increased to $17,551. While the improved treatment response with rTMS resulted in faster return to work for those employed, the increased time away from the workplace required when undergoing rTMS treatment itself shifted the balance toward higher indirect costs in the rTMS cohort.

Threshold analyses (based on direct medical costs only) were calculated to determine at what cost per-session of rTMS therapy must be priced to achieve cost neutrality and a cost/QALY gained of $100,000. At $104 per session, the cost/QALY gained is equal to $100,000; this per-session cost is approximately one-half of that estimated in the primary analysis ($206 per session). The difference in total costs of usual care and rTMS was zero at an estimated rTMS cost per session of $16. In each analysis, all other parameters were held constant.
Table 11. Cost-effectiveness of rTMS vs. usual care in patients with TRD over 5 years.

<table>
<thead>
<tr>
<th>Clinical Outcomes for 1000 patients</th>
<th>Usual Care</th>
<th>rTMS</th>
<th>Difference TMS relative to Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Treatment Response</td>
<td>2,632</td>
<td>2,993</td>
<td>360</td>
</tr>
<tr>
<td>Remission</td>
<td>2,421</td>
<td>2,806</td>
<td>385</td>
</tr>
<tr>
<td>Deaths</td>
<td>69</td>
<td>69</td>
<td>0.0</td>
</tr>
<tr>
<td>Life years</td>
<td>4,855</td>
<td>4,855</td>
<td>0.0</td>
</tr>
<tr>
<td>Quality adjusted life years (QALYs)</td>
<td>3,621</td>
<td>3,640</td>
<td>19.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative Costs for 1000 patients</th>
<th>Usual Care</th>
<th>rTMS</th>
<th>Difference TMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTMS therapy</td>
<td>$0</td>
<td>$4,918,352</td>
<td>$4,918,352</td>
</tr>
<tr>
<td>Outpatient &amp; ER costs</td>
<td>$43,320,644</td>
<td>$42,787,610</td>
<td>($533,033)</td>
</tr>
<tr>
<td>Inpatient costs</td>
<td>$9,668,104</td>
<td>$9,285,806</td>
<td>($382,299)</td>
</tr>
<tr>
<td>Total Direct Medical Costs only</td>
<td>$31,296,246</td>
<td>$35,549,730</td>
<td>$4,253,483</td>
</tr>
<tr>
<td>Indirect Non-Medical costs</td>
<td>$17,216,215</td>
<td>$19,537,966</td>
<td>$2,321,751</td>
</tr>
<tr>
<td>Total including Indirect costs</td>
<td>$70,204,963</td>
<td>$76,529,734</td>
<td>$6,324,770</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total cost per Patient</th>
<th>Usual Care</th>
<th>rTMS</th>
<th>Difference TMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Including Indirect costs</td>
<td>$70,205</td>
<td>$76,530</td>
<td>$6,325</td>
</tr>
<tr>
<td>Direct Medical Costs</td>
<td>$31,296</td>
<td>$35,550</td>
<td>$4,253</td>
</tr>
<tr>
<td>Life years per patient</td>
<td>4.85</td>
<td>4.85</td>
<td>0.00</td>
</tr>
<tr>
<td>QALY per patient</td>
<td>3.62</td>
<td>3.64</td>
<td>0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost-Effectiveness</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost/LYG</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost/QALY (direct costs only)</td>
<td></td>
<td></td>
<td>$216,468</td>
</tr>
<tr>
<td>Cost/QALY (including indirect costs)</td>
<td></td>
<td></td>
<td>$321,880</td>
</tr>
<tr>
<td>Cost/Additional Treatment Response (direct costs only)</td>
<td></td>
<td></td>
<td>$11,803</td>
</tr>
<tr>
<td>Cost/Additional Treatment Response (including indirect costs)</td>
<td></td>
<td></td>
<td>$17,551</td>
</tr>
</tbody>
</table>

1HAM-D17 < 8, HAM-D21 < 10, or MADRS < 8.
2Total direct medical costs is not equal to the sum of the components as it is discounted, whereas the components are undiscounted.
3Indirect costs include lost wages and payments from disability insurance.
Table 2 (reference copy). General model input parameters.

<table>
<thead>
<tr>
<th>Unit Item</th>
<th>Input</th>
<th>Unit</th>
<th>Frequency</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male patients</td>
<td>30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age: Male/Female</td>
<td>45.5/45.4</td>
<td>Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-Time</td>
<td>71.10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part-Time</td>
<td>15.60%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>8.10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td>5.10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Payment Items – Private</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient Visits</td>
<td>$584</td>
<td>per visit</td>
<td>2.4</td>
<td>per year</td>
</tr>
<tr>
<td>Office Visits</td>
<td>$115</td>
<td>per visit</td>
<td>13.7</td>
<td>per year</td>
</tr>
<tr>
<td>Emergency Department</td>
<td>$1,089</td>
<td>per visit</td>
<td>0.3</td>
<td>per year</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>$60</td>
<td>per script</td>
<td>31.2</td>
<td>per year</td>
</tr>
<tr>
<td>ECT</td>
<td>$433.58</td>
<td>per session</td>
<td>8</td>
<td>per course of therapy</td>
</tr>
<tr>
<td>rTMS planning</td>
<td>$246</td>
<td>per session</td>
<td>1</td>
<td>per course of therapy</td>
</tr>
<tr>
<td>rTMS delivery</td>
<td>$206</td>
<td>per session</td>
<td>20</td>
<td>per course of therapy</td>
</tr>
<tr>
<td>Inpatient Facility Admission</td>
<td>$11,296</td>
<td>per admission</td>
<td>0.1</td>
<td>admissions per year</td>
</tr>
<tr>
<td>Inpatient Professional Visit</td>
<td>$330</td>
<td>per visit</td>
<td>4.7</td>
<td>visits per admission</td>
</tr>
<tr>
<td><strong>Indirect Cost Items</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional employment wage</td>
<td>$23.57</td>
<td>per hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional disability benefit</td>
<td>$962.58</td>
<td>per month</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reason for Productivity Loss</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General depression overall</td>
<td>51.2</td>
<td>Days lost/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Medically-related</td>
<td>13.5</td>
<td>Days lost/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Disability</td>
<td>37.7</td>
<td>Days lost/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual care</td>
<td>0</td>
<td>Additional days lost/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rTMS treatment</td>
<td>11</td>
<td>Days lost/course of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Utility Items</strong></td>
<td></td>
<td></td>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>Baseline TRD - Male</td>
<td>0.708</td>
<td>Annual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline TRD – Female</td>
<td>0.708</td>
<td>Annual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>Annual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change due to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Aging</td>
<td>-0.00251</td>
<td>Annual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– ECT</td>
<td>0</td>
<td>Per course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– rTMS</td>
<td>0</td>
<td>Per course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Usual care</td>
<td>0</td>
<td>Per course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Response</td>
<td>0.0625</td>
<td>Per response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Remission</td>
<td>0.125</td>
<td>Per remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Relapse</td>
<td>-0.0625</td>
<td>Per relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Serious Adverse Event</td>
<td>-0.1</td>
<td>Per event</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.3 Conclusions

A 10% uptake in coverage of rTMS is projected to impact payer expenditures by 1.1 - 3.1% across New England, depending on whether rTMS replaces a portion of ECT use or is additive. On a per member per month (PMPM) basis, the impact ranges from $0.21 - $0.59, or a relatively modest 0.07 - 0.2% increase. Higher PMPM estimates were observed for the Medicaid-only population (0.3 - 0.5%), but remained modest. While actual decisions regarding whether to provide coverage for rTMS will require consideration of the tradeoffs involved by individual public and private payers in each state, the overall analysis presented here should be of some assistance.

In trials and in this economic evaluation, rTMS therapy is associated with improved clinical outcomes relative to usual care. The estimated cost of a course of rTMS is $4,366 per patient which is projected to be partially offset by a reduction in resource use associated with improved outcomes. Achievement of a cost/QALY below $100,000 requires a projected 50% decrease in the cost of each rTMS treatment session relative to the base case estimate. Cost neutrality cannot be achieved with a singular change in payments unless one is willing to accept a 97% decrease in the cost of each rTMS session.

These results are subject to the assumptions underlying the model and must be interpreted with care. The AHRQ review (Gaynes, 2011) determined that, in general, existing evidence is still insufficient to draw conclusions regarding the comparative effectiveness of nonpharmacologic therapies such as rTMS and ECT. The outcomes associated with these strategies and with usual care were determined by data from the relatively few studies that were feasible to quantitatively analyze in the AHRQ review (Gaynes, 2011). The strongest evidence was for the relative outcomes of rTMS compared with usual care based on the meta-analyzed data in the report. In the budget impact analysis, data were too sparse to draw meaningful inferences about the relative outcomes, thus ECT and rTMS are assumed to be equivalent on response, remission, and relapse.

Another limitation of the model is that the long-term data to inform the subsequent course of therapy following treatment success or failure with ECT and rTMS are generally unavailable; so many assumptions were required to predict outcomes beyond the first 6-12 months following treatment. Moreover, management of TRD is often complex and highly variable across patients, and even the definition of TRD itself was inconsistent across studies, leading to significant challenges in defining the course of patients over time. Finally, the underlying resource use and payments were determined from a population of insured patients diagnosed with depression in the Northeastern U.S.; while these data are somewhat relevant, they may not be completely generalizable to each state’s target population or to a more severe cohort of patients with TRD.

Taken as a whole, the model results provide an estimate of the impact of introducing rTMS therapy for CEPAC consideration. Specific point estimates should not be interpreted as absolute, rather as a guide for consideration of various scenarios that would involve the introduction of coverage for rTMS.
5.4 Comparison of ICER Analysis to Published Cost-Effectiveness Analyses

A single published study compared the cost-effectiveness rTMS to usual care (or “sham”) with results ranging from an rTMS strategy resulting in overall cost savings to a cost per QALY gained of US$36,551 (Simpson, 2009). Results were highly dependent on the source of effectiveness data – randomized control trial vs. open-label study – and the inclusion of indirect, productivity costs. The primary reason for differences between these results and ours is that Simpson and colleagues had access to primary patient level data from which to derive more specific patient response categories (i.e., category of improvement in depression score) and other key inputs, as well, an estimation of model outcomes over a one-year time horizon compared with our five-year perspective. The mean cost of rTMS therapy in this study was US$7,792 as compared to our estimated cost of $4,366. This is likely due to the longer rTMS duration assumed by Simpson and colleagues.

Other published studies (McLoughlin, 2007, Knapp, 2008) compared the cost-effectiveness of ECT to rTMS. As these were conducted from the perspective of the health system in the United Kingdom, it is difficult to draw meaningful comparisons to their estimates given the inherent differences in health-system dynamics and cost.
6. Questions and Discussion

CEPAC members voted on questions concerning the comparative clinical effectiveness of the treatment options discussed: 1) repetitive transcranial magnetic stimulation (rTMS) and 2) electroconvulsive therapy (ECT).

- **Comparative clinical effectiveness: rTMS vs. usual care**

  For patients who have TRD, 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)?

  **CEPAC Vote: 10 Yes 5 No**

  a. If yes:
  - Is rTMS equivalent or superior to usual care?
    - 5 Equivalent 5 Superior
  
  b. If no, is this due to:
  - Inadequate evidence with which to judge comparative net health benefit
    - 5 Yes
  - Adequate evidence of an inferior net health benefit
    - 0 Yes

  **Comments:**

  - CEPAC desired greater clarity on the ideal number of treatment failures required before rTMS is used, since standard practice differs from the FDA label (one failed trial of antidepressants).
  - Although the majority of CEPAC voted that the evidence is adequate to suggest that rTMS is more effective than usual care, comments from some CEPAC members noted the need for more data on which patients are ideal candidates for rTMS.
  - Some members expressed concern about the potential for overutilization of rTMS without a standard definition of the ideal patient population.
  - Many CEPAC members who voted that the evidence was inadequate to determine if rTMS is as effective or better than usual care cited the dearth of evidence on the benefits of rTMS beyond the initial 4-6 week treatment phase.

- **Comparative clinical effectiveness: rTMS vs. ECT**

  For patients who have TRD, is the evidence adequate to demonstrate that rTMS provides a net health benefit equivalent or superior to ECT?
CEPAC Vote: 9 Yes 6 No

a. If yes:
   - Is rTMS equivalent or superior to ECT?
     9 Equivalent 0 Superior

b. If no, is this due to:
   - Inadequate evidence with which to judge comparative net health benefit
     6 Yes
   - Adequate evidence of an inferior net health benefit
     0 Yes

Comments:
   - CEPAC emphasized the need to identify the subpopulations that would benefit more from each therapy. Some CEPAC members suggested the need to establish target subpopulations for each treatment, with more severe patients receiving ECT and less severe patients receiving rTMS.

Comparative Value

When a majority of CEPAC votes that the evidence is adequate to demonstrate that an intervention produces patient outcomes equivalent or superior to a reference option, the Council members are also asked to vote on whether the intervention represents a “high,” “reasonable,” or “low” value. The value “perspective” that members of CEPAC are asked to assume is that of a state Medicaid program that must make resource decisions within a fixed budget for care. While information about hypothetical budget tradeoffs are provided, CEPAC is not given prescribed boundaries or thresholds for budget impact, PMPM changes, or incremental cost-effectiveness ratios to guide its judgment of high, reasonable, or low value. For each vote on comparative value Council members are asked to complete a multi-criteria decision analysis scoring sheet to make more transparent how they weighed different criteria in their ultimate judgment of comparative value. Only those CEPAC members who vote that the evidence is adequate to demonstrate equivalent or superior clinical effectiveness are asked to vote on comparative value.

Votes on Comparative Value

In response to public comment provided in advance of the December 9 meeting, an additional analysis was conducted prior to voting. The comment suggested that a more relevant comparison might be the use of rTMS as an adjunct to usual care vs. usual care with another adjunctive therapy (e.g., CBT, adding an antipsychotic drug). A simple calculation was made to address this by adding the median cost of antipsychotic therapy observed in a TRD cohort study (Ivanova, 2010) and applying it to the cost-effectiveness model; no change in effectiveness was assumed. Over 5 years,
this change would be estimated to increase the direct cost of usual care to approximately $3,370 per patient, thereby decreasing the incremental cost of rTMS to approximately $1,900, and the resulting cost per QALY gained to $98,000.

1. **rTMS vs. usual care**
   Based on reimbursement levels provided with this report, would you judge the comparative value of rTMS to be of 1) high value; 2) reasonable value; or 3) low value compared to usual care?

   **CEPAC Vote:** 4 Low 6 Reasonable

2. **rTMS vs. ECT**
   Based on reimbursement levels provided with this report, would you judge the comparative value of rTMS to be of 1) high value; 2) reasonable value; or 3) low value compared to ECT?

   **CEPAC Vote:** 5 Low 3 Reasonable 1 High

**Social value considerations for policymakers**

The final question of the meeting explored broader considerations of public health, equity, and access:

- Are there any considerations related to public health, equity, disparities in access or outcomes for specific patient populations, or other social values that should be considered in medical policies related to the use of rTMS, ECT, VNS, or CBT/IPT?

CEPAC voiced concern that with no third party reimbursement for rTMS, only patients who can afford to pay out-of-pocket can obtain treatment. Therefore, there may be concerns over equity in access to rTMS for certain populations.

**Roundtable Discussion**

Following the CEPAC votes and deliberation of the evidence, CEPAC engaged in a roundtable discussion with a panel composed of two representatives from the clinical expert community and two representatives of regional private health plans. The goal of the roundtable was to explore the implications of CEPAC votes for clinical practice and payer policies. The topics discussed included:

**Future Research**

Panelists outlined the gaps in current evidence and outlined future research needs to support future coverage decisions, including evidence of the long-term health benefit and duration of effect for rTMS. Panelists also indicated their concern for the shortage of funding for these types of clinical trials.

**Coverage considerations**

Payer representatives and CEPAC discussed the prospect of using specific medical policies for rTMS such as coverage with evidence development, patient registries, and limited networks with centers of excellence, but voiced concern for the practicalities of each. Payers at the table cautioned that with such a significant population in need of interventions to treat resistant-depression, that centers of excellence and limited networks may not be able to accommodate the demand for these
services, and that payers will have to be able to prioritize which patients receive treatment if coverage becomes available.

Payers also stressed their concerns for indication creep if rTMS became available for everyone to use, highlighting that without further evidence on the specifics of treatment duration, maintenance therapy, and selection in the appropriate patient population, that rTMS could be used inappropriately.

**Policy Implications:**

**Physician Specialty Societies**

- Professional societies should lead the effort in establishing training and practice standards and promote the development of registries to monitor outcomes of patients receiving treatment for TRD that can be used to guide quality improvement.
- Professional societies should develop clinical guidelines for TRD that include recommendations for: 1) the appropriate subpopulations to receive treatment with rTMS and ECT; 2) treatment duration and frequency for rTMS; 3) maintenance therapy requirements; and 4) the threshold for previously failed treatments required before considering rTMS.

**Hospitals and other clinical providers**

- Each hospital providing treatment for TRD should participate in registries to gather data on the short and long-term outcomes of patients undergoing ECT or rTMS. The data derived from these registries should be used to guide internal quality improvement and inform the appropriateness of each therapy for various subpopulations as well as an evaluation of the long-term outcomes for patients receiving treatment for TRD.

**Payers**

- If payers elect to cover rTMS, they should consider limiting coverage to patients with ≥ 2 failed drug treatments during the most recent episode of depression, a higher threshold than that included in the FDA license. In addition, payers should consider options for limiting coverage to designated centers of excellence, perhaps with an additional requirement for continued evidence generation through a national registry to be organized by professional societies. These limitations would be useful to assure the following: 1) consistent, rigorous training standards are established for providers; and 2) coverage will support rather than hinder efforts to gather further evidence to help guide future patient, provider, and payer decisions regarding appropriate patient selection for both rTMS and ECT. Payers on the roundtable voiced concerns for the feasibility and practicality of a centers of excellence approach for coverage of rTMS due to the large number of patients potentially eligible for this service and the consequent difficulty of assuring equitable access. All participants on the roundtable agreed that it is difficult to find funding to support large, effective registries.
7. Public Comment

Members of the public were invited to submit public comment on the draft supplementary report during the period of November 16, 2011 to December 21, 2011. The following organizations submitted and/or presented public comments:

- David G. Brock, M.D., Medical Director, Neuronetics, Inc.
- Jeffrey C. Fetter, M.D. and Paul Holzheimer, M.D., Executive Council to the New Hampshire Psychiatric Society
- Patricia R. Recupero, J.D., M.D. President and CEO, and colleagues, Butler Hospital
- Linda Carpenter, MD, Butler Hospital

The complete statements provided to CEPAC can be accessed via the CEPAC website.
References


5. Anthem. Medical policy: Vagus nerve stimulation (SURG.00007). 

6. Anthem. Medical policy: Transcranial magnetic stimulation for depression and other neuropsychiatric disorders. 


44. Klerman GL, Weissman MM. The course, morbidity, and costs of depression. *Arch Gen Psychiatry.* 1992;49(10):831-834.


63. Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in the course of electroconvulsive therapy. Depress Anxiety. 2000;12(3):118-123.


81. U.S. Food and Drug Administration, Center for Devices and Radiological Health. Premarket approval application (PMA) supplement: VNS therapy system (Cyberonics, Inc.).


## Appendix A

<table>
<thead>
<tr>
<th>Study Citation</th>
<th>Study Characteristics</th>
<th>Patient Population</th>
<th>Study Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research Objective</strong></td>
<td><strong>Study Design:</strong> Case series</td>
<td>Depressed in-patients who had not responded to at least 4 weeks of pharmacotherapy</td>
<td><strong>Mean post-treatment GRID-HAMD score:</strong> 10.2 (p&lt;0.001)</td>
<td>No assessment conducted</td>
</tr>
<tr>
<td><strong>Author, Year:</strong> Azuma H. et al., 2011</td>
<td><strong>N=53</strong></td>
<td><strong>Mean age:</strong> 49.6 years</td>
<td><strong>Remitters (50% reduction of baseline GRID-HAMD score, and score ≤ 7 points on post-treatment GRID-HAMD score):</strong> N=16 (30.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Research Objective:</strong> Evaluation of the association of ictal peak HR and ictal EEG markers with the efficacy of ECT</td>
<td><strong>Study Duration:</strong> 20 days (10 days before and after an ECT session)</td>
<td><strong>Gender:</strong> 31 males, 22 females</td>
<td><strong>Responders (50% reduction of baseline GRID-HAMD score):</strong> N=26 (49.1%)</td>
<td></td>
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<tr>
<td></td>
<td><strong>Intervention:</strong> ECT</td>
<td><strong>Diagnosis:</strong> MDD, 49 BD, 4</td>
<td>Peak HR and postictal suppression index were associated with therapeutic efficacy in remitters with adequate seizures</td>
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<tr>
<td></td>
<td>Location: bilaterally to frontotemporal region</td>
<td><strong>Mean duration of current episode:</strong> 21.0 months</td>
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<td></td>
<td>Intensity: minimum seizure duration of 20 sec.; if missed or abortive (&lt;20 sec.), increased pulse wave stimuli by 10% up to 100%, for a maximum of 3 stimulations per session</td>
<td><strong>Mean number of previous episodes:</strong> 1.7</td>
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<td></td>
<td><strong>Medications Allowed:</strong> Antidepressants, which remained unchanged throughout study; benzodiazepines, antipsychotics, antiparkinson medications and antihypertensives allowed; lithium and anti-epileptics discontinued</td>
<td><strong>Mean pre-treatment GRID-HAMD score:</strong> 20.2</td>
<td></td>
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</tr>
</tbody>
</table>
| **Study Citation**  
**Research Objective** | **Study Characteristics** | **Patient Population** | **Study Outcomes** | **Adverse Events**  
**Quality of Life** |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| **Author, Year:**  
Baeken C. et al., 2011 | **Study Design:**  
Prospective matched cohort  
N=42 | **Group 1**  
Unipolar depressed patients of melancholic subtype  
For current depressive episode, all patients had at least 2 unsuccessful trials of SSRI/SNRI medications and 1 failed trial of TCA therapy  
**Overall mean age:**  
45.3 years  
**Overall gender:**  
8 males, 13 females | **Group 1**  
Responders  
(50% reduction of baseline HDRS)  
**Mean baseline HDRS score:**  
26.67  
**Mean post HDRS score:**  
9.11  
**Non-responders**  
**Mean baseline HDRS score:**  
24.75  
**Mean post HDRS score:**  
21.25 | No assessment conducted |
| **Research Objective:**  
Assessment of impact of HF rTMS therapy on post-synaptic 5-HTA<sub>2A</sub> receptor binding indices | **Study Duration:**  
At least 4 weeks (unspecified washout period, followed by 2 week period without antidepressants or psychotropic medications, then a 2 week period of rTMS sessions) | **Group 2**  
Healthy, age- and sex-matched individuals with no history of depression  
**Overall mean age:**  
42.1 years  
**Overall gender:**  
8 males, 13 females | Compared with the control group, depressed patients had less baseline 5-HTA<sub>2A</sub> receptor binding indices in the DLPFC, and higher 5-HTA<sub>2A</sub> receptor binding indices in the left hippocampus  
Better outcomes with HF-rTMS were associated with a decrease in the right hippocampal 5-HTA<sub>2A</sub> receptor binding, and positively correlated with bilateral 5-HTA<sub>2A</sub> receptor | |
| | **Intervention:**  
**Group 1**  
HF-rTMS  
Location:  
left and right DLPFC  
Frequency: 10 Hz  
Intensity: 110% of patient’s resting motor threshold  
Number of trains: 40  
Length of trains: 3.9 sec.  
Inter-train interval: 26.1 sec.  
Number of sessions: 10 daily, over 2 week | | | |
| | **Medications Allowed:**  
Benzodiazepines; all antidepressants and psychotropic agents were | | | |
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<tr>
<th>Study Citation Research Objective</th>
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<tbody>
<tr>
<td><strong>Author, Year:</strong> Berlim M. et al, 2011</td>
<td>discontinued Group 2 No intervention</td>
<td>Patients with moderate to severe MD and current diagnosis of a moderate current major depressive episode</td>
<td>binding indices in the DLPFC</td>
<td>1 patient withdrew because of scalp pain</td>
</tr>
<tr>
<td><strong>Research Objective:</strong> Evaluation of HF-rTMS as an augmenting therapy over a broad range of clinical and subjective outcomes in treatment-resistant MDD</td>
<td><strong>Study Design:</strong> Case series N=15 <strong>Study Duration:</strong> 4 weeks <strong>Intervention:</strong> HF rTMS Location: left DLPFC Frequency: 10 Hz Intensity: 120% of resting motor threshold Number of trains: 75 Length of trains: 4 sec. Inter-train interval: 26 sec. Number of sessions: 5 daily per week for a total of 20 sessions <strong>Medications Allowed:</strong> Current stable doses of psychotropic medications, and benzodiazepines, which were titrated as needed</td>
<td>Patients had failed to respond to at least 3 courses of antidepressants from at least 2 different classes during current episode</td>
<td>Mean post-treatment HAM-D21: 25.27 (p=0.035) Significant reductions were also measured in the IDS-SR30, HAM-A, BAI and CGI-S scales</td>
<td>Mean post-treatment WHOQOL-Bref – physical QOL: 39.12 (p=0.028)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age: 47 years Gender: 7 males, 8 females Mean duration of current episode: 68 months Mean number of previous episodes: 1.53 Mean pre-treatment HAM-D21: 29.87</td>
<td></td>
<td>Mean post-treatment WHOQOL-Bref – psychological QOL: 28.61 (p=0.041) Significant improvement was seen in the WHOQOL-Bref – overall QOL No significant changes were noted in the social and environmental domains of the WHOQOL-Bref.</td>
</tr>
<tr>
<td><strong>Study Citation</strong></td>
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<tr>
<td><strong>Author, Year:</strong> Domschke K. et al., 2010</td>
<td>Analysis of the effects on ECT response in TRD patients with the COMT val158met genotypic polymorphism</td>
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<tbody>
<tr>
<td><strong>Study Design:</strong> Case series</td>
<td><strong>N=104</strong></td>
<td>Patients with current major depression with pharmacologically treatment-resistant disease, having failed at least 2 courses of antidepressant therapy</td>
<td>Mean pre-treatment WHOQOL-Bref – physical QOL: 32.85</td>
<td>No analysis conducted</td>
</tr>
<tr>
<td><strong>Study Duration:</strong> Ranging from a mean of 7.6 to 8.4 weeks</td>
<td><strong>Intervention:</strong> ECT</td>
<td><strong>Mean age:</strong> 56.6 years</td>
<td>Mean post-treatment HAM-D21: 9.1 (p&lt; 0.0005)</td>
<td></td>
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<tr>
<td><strong>Location:</strong> right, unilateral (6 patients switched to bilateral therapy due to insufficient response)</td>
<td><strong>Intensity:</strong> minimum seizure duration of 25 sec.; restimulation included dosage elevation in 5-10% steps</td>
<td><strong>Gender:</strong> 33 males, 71 females</td>
<td><strong>Responders:</strong> (&gt;50% reduction of HAM-D) 67/104</td>
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<tr>
<td><strong>Medications Allowed:</strong> Antidepressants, neuroleptics and anxiolytics</td>
<td><strong>Mean number of previous episodes:</strong> 3.7</td>
<td><strong>Non-responders:</strong> (≤ 50% decrease in HAM-D) 37/104</td>
<td>The more active allele of COMT 158val was significantly associated with pre-ECT severity of depression, particularly in female patients; these carriers also responded significantly better to ECT therapy</td>
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<tr>
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<tr>
<td><strong>Author, Year:</strong> Holtzheimer P.E. et al., 2010</td>
<td><strong>Study Design:</strong> Case series</td>
<td>Depressed patients in a current major depressive episode, with ≤ 3 adequate medication failures in current episode</td>
<td>At 6 weeks (n=9): 1. <strong>Mean HDRS24:</strong> 11.1 (p&lt; 0.001) 2. <strong>Responders:</strong> (≥ 50% decrease in baseline HDRS24) 5/14 3. <strong>Remitters:</strong> (HDRS24 ≤ 10) 4/14</td>
<td>1 patient discontinued the trial due to increased suicidal ideation 1 patient required a decrease in stimulation intensity due to tolerability and subsequently dropped out of the trial</td>
</tr>
<tr>
<td><strong>Research Objective:</strong> Evaluation of the safety and efficacy of accelerated rTMS (aTMS) in depressed patients</td>
<td><strong>N=14</strong></td>
<td><strong>Median age:</strong> 51 years (range 20-74)</td>
<td><strong>Responders:</strong> (≥ 50% decrease in baseline HDRS24) 5/14</td>
<td>No seizures occurred</td>
</tr>
<tr>
<td><strong>Study Duration:</strong> 6 weeks</td>
<td><strong>Gender:</strong> 9 males, 5 females</td>
<td><strong>Mean HDRS24:</strong> 11.1 (p&lt; 0.001)</td>
<td><strong>Remitters:</strong> (HDRS24 ≤ 10) 4/14</td>
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</tr>
<tr>
<td><strong>Intervention:</strong> aTMS</td>
<td><strong>Diagnosis:</strong> MDD, 13 BD, 1</td>
<td>Significant decreases were noted in HAM-A, RBANS and BDI</td>
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<tr>
<td>Location: left DLPFC</td>
<td><strong>Median duration of current episode:</strong> 9 months (range 3-96)</td>
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<tr>
<td><strong>Frequency:</strong> 10 Hz</td>
<td><strong>Median number of previous episodes:</strong> 4 (range 2-8)</td>
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<tr>
<td><strong>Intensity:</strong> 100% of motor threshold</td>
<td><strong>Mean baseline HDRS24 score:</strong> 24.6</td>
<td></td>
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<tr>
<td><strong>Number of trains:</strong> 20 per hour-long session</td>
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<td><strong>Length of trains:</strong> 5 sec.</td>
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<tr>
<td><strong>Inter-train interval:</strong> 25 sec.</td>
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<tr>
<td><strong>Number of sessions:</strong> 5 consecutive sessions on Day 1; 10 consecutive sessions on Day 2</td>
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<tr>
<td><strong>Medications Allowed:</strong> No specific restrictions; patients needed to maintain stable dosing throughout study</td>
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</tbody>
</table>
| **Author, Year:** Jhanwar V.G. et al., 2011 | **Study Design:** Case series  
**N= 21**  
**Study Duration:** 4 weeks  
**Intervention:** rTMS  
**Location:** left DLPFC  
**Frequency:** 10 Hz  
**Intensity:** 110% of patient’s motor threshold  
**Number of trains:** 25 Length of trains: 5 sec.  
**Inter-train interval:** 25 sec.  
**Number of sessions:** 20 sessions over 4 weeks  
**Medications Allowed:** No specific restrictions, except no changes were allowed after inclusion into the study | Patients with MDD, without psychotic features, with at least 2 adequate trials of antidepressants  
**Mean age:** 38 years  
**Gender:** 13 males, 8 females  
**Mean duration of current episode:** 36.57 months  
**Mean baseline HAM-D17 score:** 30.80 | **Mean post-treatment HAM-D17 score:** 19.00 (p< 0.001)  
A significant decrease in CGI-C was also noted. | No study dropouts were due to adverse events.  
4 patients reported headache and pain over left scalp during treatment that ceased with termination of rTMS  
No patients developed new onset of seizures  
There were no patient reports of memory or cognitive side effects  
There was no impact of rTMS on blood pressure or heart rate during treatment |
<table>
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<tr>
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<tbody>
<tr>
<td><strong>Research Objective:</strong> Analysis of changes in cerebral blood flow following low-frequency right prefrontal stimulation (LFRS) and neuroanatomical correlates of therapeutic efficacy in patients with TRD</td>
<td><strong>Study Design:</strong> Case series</td>
<td>Patients diagnosed with MDD (unipolar) with failed response to a minimum of 2 courses of antidepressants from different classes, in the current episode</td>
<td><strong>Mean post-treatment HDRS score:</strong> 11.92 (p&lt; 0.001)</td>
<td>No analysis conducted</td>
</tr>
<tr>
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<td><strong>N=26</strong></td>
<td></td>
<td><strong>Responders:</strong> (50% reduction in HDRS from baseline)</td>
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<tr>
<td></td>
<td><strong>Study Duration:</strong> 5 weeks</td>
<td></td>
<td><strong>Remitters:</strong> (HDRS &lt;8)</td>
<td>11/26</td>
</tr>
<tr>
<td></td>
<td><strong>Intervention:</strong> rTMS</td>
<td></td>
<td><strong>Non-responders:</strong></td>
<td>4/11 responders</td>
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<tr>
<td></td>
<td>Location: right DLPFC</td>
<td></td>
<td></td>
<td>15/26</td>
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<tr>
<td></td>
<td>Frequency: 1 Hz</td>
<td></td>
<td><strong>No areas with significantly increased cerebral blood flow were identified following LFRS</strong></td>
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<td></td>
<td>Intensity: 100% of resting motor threshold</td>
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<td><strong>Significant decreases were seen in regional cerebral blood flow, with correlation to therapeutic efficacy of LFRS in areas such as the right prefrontal cortex and the bilateral orbitofrontal cortex</strong></td>
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<td>Number of trains: 5</td>
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<td>Length of trains: 60 sec.</td>
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<td>Inter-train interval: 60 sec.</td>
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<td>Number of sessions: 12 sessions over 3 weeks</td>
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<tr>
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<td><strong>Medications Allowed:</strong> No specific restrictions; however no changes allowed 4 weeks prior to, and throughout study</td>
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<tr>
<td><strong>Study Citation</strong> Research Objective</td>
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</table>
| **Author, Year:** Minelli A. et al., 2011 | **Study Design:** Case series  
**N=19**  
**Study Duration:** 1 month  
**Intervention:** ECT  
**Location:** bilateral frontotemporal region  
**Intensity:** NR  
**Conditions:** Max charge, 504 mC  
Current, 0.9 A  
Frequency 30-70 Hz  
Pulse width, 1 ms  
Max duration 8 sec.  
**Medications Allowed:** Concurrent medications maintained for 3 weeks prior to and throughout study | **Patients with TRD MDD (unipolar) with failure to respond to at least 2 adequate trials of 2 or more antidepressants classes, and to an adequate trial of a TCA**  
**Mean age:** 54.84 years  
**Gender:** 4 males, 15 females  
**Mean baseline MADRS:** 34.32 | **Mean post-treatment MADRS:** 7.42 (p< 0.001)  
VEGF serum concentrations significantly increased from baseline to the end of the study  
A significant correlation was found between the increase in VEGF at 1 month and the decrease in MADRS score | No analysis conducted |
<table>
<thead>
<tr>
<th>Study Citation Research Objective</th>
<th>Study Characteristics</th>
<th>Patient Population</th>
<th>Study Outcomes</th>
<th>Adverse Events Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, Year: Oulis P. et al., 2011</td>
<td>Study Design: Case series</td>
<td>Patients with MDD and resistant to combination therapy with antidepressant and atypical antipsychotic medications</td>
<td>QTc interval changes remained within normal limits just prior to and throughout ECT administration (up to 10 minutes afterwards)</td>
<td>No adverse cardiac events occurred in patients, including arrhythmias such as torsade de pointes</td>
</tr>
<tr>
<td>Research Objective: Investigation of QTc interval changes associated with concomitant ECT and atypical antipsychotic/antidepressant therapy</td>
<td>N=6</td>
<td>Mean age: 50 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Duration: 10 to 11 sessions</td>
<td>Gender: 6 females</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intervention: ECT Location: bilateral application, location NR Intensity: NR Medications Allowed: All patients received antidepressant therapy along with low doses of atypical antipsychotics</td>
<td></td>
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</tr>
</tbody>
</table>
**Study Citation**

Research Objective: Assessment of gustatory and olfactory perception during VNS therapy in patients with refractory depression

<table>
<thead>
<tr>
<th>Study Citation</th>
<th>Study Characteristics</th>
<th>Patient Population</th>
<th>Study Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author, Year:</strong> Sperling W. et al., 2011</td>
<td><strong>Study Design:</strong> Case series</td>
<td>Therapy-resistant patients with a major depressive episode</td>
<td>No statistically significant changes assessed during on and off mode VNS therapy</td>
<td>No analysis conducted</td>
</tr>
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<td><strong>Research Objective:</strong></td>
<td><strong>N=9</strong></td>
<td></td>
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<tr>
<td></td>
<td><strong>Study Duration:</strong> NR</td>
<td><strong>Mean age:</strong> 51.6 years</td>
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<td></td>
<td><strong>Intervention:</strong> VNS</td>
<td><strong>Gender:</strong> 6 males, 3 females</td>
<td>Significant changes in the intensity of taste perception were demonstrated during the on mode of VNS, particularly with “sweet” and “bitter”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intensity: 1.25 mA</td>
<td><strong>Mean baseline HAM-D17 score:</strong> 10.89</td>
<td></td>
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<tr>
<td></td>
<td>Frequency: 20 Hz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulse width: 500 μs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>On mode: 30 sec. on, 5 min. off</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Off mode: 30 min. off</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>Medications Allowed:</strong> No concurrent medications allowed 2 weeks prior to and throughout study</td>
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</tbody>
</table>

**Abbreviations:**

5-HTA2A: a serotonin receptor; A: amps; aTMS: accelerated repetitive transcranial magnetic stimulation; BAI: Beck Anxiety Inventory; BD: bipolar disorder; BDI: Beck Depression Inventory-2; CGI-C: Clinical Global Impression - change subscale; CGI-S: Clinical Global Impression-severity subscale; COMT: catechol-O-methyltransferase; DLPFC: dorsolateral pre-frontal cortex; ECT: electroconvulsive therapy; EEG: electroencephalogram; GRID-HAMD: standardized administration and scoring of the HAMD; HAM-A: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; HDRS: Hamilton Depression Rating Scale; HF: high frequency; HR: heart rate; Hz: herz; IDS-SR30: 30 item Inventory of Depressive Symptomatology; LFRS: low-frequency right pre-frontal stimulation; MADRS: Montgomery and Asberg Depression and Rating Scale; mC: milliCoulomb; MDD or MD: major depressive disorder; ms: millisecond; NR: not reported; QOL: quality of life; QTc: corrected QT interval; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; rTMS: repetitive transcranial magnetic stimulation; TCA: tricyclic antidepressant; TRD: treatment-resistant depression; VEGF: vascular endothelial growth factor; VNS: vagus nerve stimulation; WHOQOL: World Health Organization’s quality of life measure, brief version.
Overview of the CEPAC Initiative
The New England Comparative Public Advisory Council (CEPAC)

**Mission:** The purpose of the New England Comparative Effectiveness Public Advisory Council (CEPAC) is to aid patients, physicians and policymakers in New England in the application and use of comparative effectiveness information to improve the quality and value of healthcare in the region. In partnership with the Institute for Clinical and Economic Review, based at the Massachusetts General Hospital’s Institute for Technology Assessment, CEPAC is tasked with aiding in the adaptation and dissemination of federally-produced comparative effectiveness information. The mission is to produce actionable information to aid regional policymakers in the medical policy decision-making process. CEPAC is an independent body of 19 members, composed of clinicians and patient or public representatives from each New England state with skills in the interpretation and application of medical evidence in health care delivery. Representatives of state public health programs and of regional private payers are included as ex-officio members of CEPAC. The latest information on the project is available online: cepac.icer-review.org.

**Process:** CEPAC meets twice a year to review timely comparative effectiveness research, comment on its relevance for the six New England states; and aid in the dissemination of the information to policymakers and decision-makers throughout New England. During these public meetings, CEPAC is presented with an adapted evidence review and public comments; deliberates and votes on key questions related to comparative clinical effectiveness and value; and discusses and debates the implications of the council votes with a panelist of payer and clinical stakeholders, highlighting key avenues for implementation of the evidence. The deliberations and decisions of CEPAC are conducted in a public forum to ensure transparency and accountability to all stakeholders throughout the process.

**Impact:** The Medicare Administrative Contractor for most of New England, NHIC, Corp, recently issued a final local coverage decision granting first-in-the-nation Medicare coverage for repetitive transcranial magnetic stimulation (rTMS) for patients with treatment-resistant depression. The new coverage policy, which took effect in March 2012, reversed a non-coverage draft policy posted in November 2011, and represents the first positive local Medicare coverage policy for rTMS in the nation. In describing the factors considered for this policy change, the Medicare Contractor cited numerous comments and statements received from patients and clinicians, several of which cited the comparative effectiveness review produced by the federal Agency for Healthcare Research and Quality (AHRQ), supplementary analyses of this report prepared for the New England Comparative Effectiveness Public Advisory Council (CEPAC), and the votes taken by CEPAC as part of its public deliberation on the evidence (read the press release).