HEALTH EVIDENCE REVIEW COMMISSION (HERC)

DRAFT COVERAGE GUIDANCE: NON-PHARMACOLOGIC INTERVENTIONS FOR TREATMENT RESISTANT DEPRESSION

DATE: XX/XX/XXXX

HERC COVERAGE GUIDANCE

In patients with an episode of major depressive disorder who have failed an initial trial of antidepressants, psychotherapy should be covered.

In patients with an episode of major depressive disorder who have failed at least two or more pharmacologic treatments the following treatments should be covered:

1) Repetitive transcranial magnetic stimulation
2) Electroconvulsive therapy

Vagus nerve stimulation should not be covered.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

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EVIDENCE SOURCE

Gaynes, B.N., Lux, L., Lloyd, S., Hansen, R.A., Gartlehne, G., Thieda, P., et al. (2011). *Nonpharmacologic interventions for treatment-resistant depression in adults. Comparative effectiveness review no. 33.* (Prepared by RTI International-University of North Carolina [RTI-UNC] Evidence-Based Practice Center under Contract No. 290-02-0016I.) AHRQ Publication No. 11-EHC056-EF. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from www.effectivehealthcare.ahrq.gov/reports/final.cfm

Trivedi, R.B., Nieuwsma, J.A., Williams, J.W., & Baker, D. (2009). *Evidence synthesis for determining the efficacy of psychotherapy for treatment resistant depression.* Washington, DC: Department of Veterans Affairs Veterans Health Administration Health Services Research & Development Service. Retrieved from http://www.hsrd.research.va.gov/publications/esp/Depression-Q3.pdf

The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

SUMMARY OF EVIDENCE

Clinical Background

Major depressive disorder is common and costly. Over the course of a year, between 13.1 million and 14.2 million people will experience major depressive disorder. Approximately half of these people seek help for this condition, and only 20% of those receive adequate treatment. For those who do initiate treatment for their depression, approximately 50% will not adequately respond following acute phase treatment. Patients with two or more prior treatment failures are considered to have treatment-resistant depression. Patients with treatment-resistant depression incur the highest direct and indirect medical costs among those with major depressive disorder. These costs increase with the severity of treatment-resistant depression. Treatment-resistant patients are twice as likely to be hospitalized, and their cost of hospitalization is more than six times the mean total costs of depressed patients who are not treatment resistant.

Given the burden of treatment-resistant depression generally, the uncertain prognosis of the disorder, and the high costs of therapy, clinicians and patients alike need clear evidence to guide their treatment decisions. Somatic treatments, which may involve use of a pharmacologic intervention or a device, are commonly considered for patients with treatment-resistant depression. Antidepressant medications, which are the most commonly used intervention, have decreasing efficacy for producing remission after patients have experienced two treatment failures. Such drugs also often have side effects, sometimes minor but sometimes quite serious. For these reasons, clinicians often look for alternative strategies for their treatment-resistant depression patients.

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Evidence Review

The Gaynes 2011 review provides a comprehensive summary of the available data addressing the comparative effectiveness of four nonpharmacologic treatments as therapies for adult patients with treatment-resistant depression: electroconvulsive therapy, repetitive transcranial magnetic stimulation, vagus nerve stimulation, and cognitive behavioral therapy or interpersonal psychotherapy. While the definition of treatment resistant depression remains controversial, it is defined in this report as *an episode of MDD that has not recovered following two or more adequate antidepressant medication treatments, regardless of the class of antidepressant used or whether the treatment failures were required to be in the current episode*. In addition, studies using alternate or unclear definitions are also included, although they are identified as a lower source of evidence. Results are presented as direct or indirect evidence, with direct evidence being a direct comparison between two of the four included interventions. In contrast, indirect evidence compares two or more interventions by comparing differences in effectiveness or safety of each intervention compared to placebo.

Because the Gaynes review identified no eligible trials of cognitive behavioral or interpersonal psychotherapy for their definition of treatment resistant depression, the Trivedi 2009 review was included to provide evidence about psychotherapy in adult patients who have failed at least one course of antidepressant therapy.

Gaynes 2011

Efficacy of Nonpharmacologic Interventions Against Other Nonpharmacologic Interventions

Direct evidence. The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions for treatment-resistant depression is limited to two fair trials (both in major depressive disorder-only populations). One compared electroconvulsive therapy and repetitive transcranial magnetic stimulation, and the other compared electroconvulsive therapy and electroconvulsive therapy plus transcranial magnetic stimulation. They showed, with low strength of evidence, no differences between treatment options for depressive severity, response rates, and remission rates. No trial involved a direct comparison of cognitive behavioral therapy, interpersonal psychotherapy or vagus nerve stimulation with another nonpharmacologic intervention.

Indirect evidence. We identified trials that compared a nonpharmacologic intervention, generally repetitive transcranial magnetic stimulation or vagus nerve stimulation, with a control or sham procedure. We identified no eligible electroconvulsive therapy or cognitive behavior/ interpersonal psychotherapy versus control studies that used the stricter definition of treatment resistant depression. Repetitive transcranial magnetic stimulation was beneficial relative to controls receiving a sham procedure for all three outcomes (severity of depressive symptoms, response rate, remission rate). Specifically, repetitive transcranial magnetic stimulation produced a greater decrease in depressive severity (high strength of evidence), averaging a decrease in depressive severity measured by the Hamilton Rating Scale for Depression of more than 5 points relative to sham control, and this change meets the minimum threshold of the 3-point

rating scale difference that is considered clinically meaningful. Response rates were greater with repetitive transcranial magnetic stimulation than sham (also high strength of evidence); those receiving repetitive transcranial magnetic stimulation were more than three times as likely to achieve a depressive response as patients receiving a sham procedure. Finally, repetitive transcranial magnetic stimulation was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving repetitive transcranial magnetic stimulation were more than six times as likely to achieve remission as those receiving the sham. One good-quality vagus nerve stimulation versus sham control trial (a mixed major depressive disorder/bipolar population) reported no differences between the groups as measured by a change in depressive severity or response rates (low strength of evidence).

Efficacy of Nonpharmacologic Interventions Compared With Antidepressant Pharmacotherapies

Direct evidence. The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions compared with pharmacologic treatment (in this case, paroxetine) is limited to one fair-quality trial (a mixed major depressive disorder/bipolar population). Electroconvulsive therapy produced a significantly greater decrease in depressive severity (9 points by Hamilton Rating Scale for Depression) and significantly better response rates (71% vs. 28%) than medications (low strength of evidence).

Indirect evidence. In order to allow for comparison to non-pharmacologic therapy, mean average outcomes for pharmacologic treatments were calculated, and are presented below:

- For switching strategies[1], mean pharmacologic response rates averaged 39.8% and mean remission rates averaged 22.3%.
- For augmentation[2], mean response rates averaged 38.1% and mean remission rates averaged 27.2%.
- For maintenance strategies, mean response rates averaged 27.3% and mean remission rates averaged 16.8%.

Although these results provide an idea of the general degree of response seen with next-step pharmacologic treatment in treatment-resistant depression, they serve as an uncontrolled case series and should be compared to nonpharmacologic outcomes only with caution.

Maintenance of Remission or Prevention of Relapse

Direct evidence. With respect to maintaining remission (or preventing relapse), there were no direct comparisons involving electroconvulsive therapy, repetitive transcranial magnetic stimulation, vagus nerve stimulation, or cognitive behavioral/ interpersonal psychotherapy.

[1] Changing from one antidepressant to another
[2] Adding a second antidepressant

Indirect evidence. Three fair trials compared repetitive transcranial magnetic stimulation with a sham procedure and found no significant differences. However, too few patients were followed during the relapse prevention phases in two of the three studies, and patients in the third received a cointervention providing insufficient evidence for a conclusion. There were no eligible studies for electroconvulsive therapy, vagus nerve stimulation, or psychotherapy.

Efficacy of Nonpharmacologic Interventions for Patients With Different Symptomatology

Direct evidence. There were no trials that addressed whether procedure-based treatments differed as a function of symptom subtypes. Also, no comparative evidence was available about psychotherapy in subgroups defined by symptom clusters.

Indirect evidence. No studies were identified that tested either procedure-based or psychotherapeutic interventions against sham procedures or other controls.

Safety, Adverse Events, and Adherence

Direct evidence. In examining safety, adverse events, and adherence, there were some differences across the interventions in the harms and negative side effects to patients. However, the data were insufficient to reach a conclusive result. For this analysis only, both clinical trials and cohort studies were included, with specific focus on cognitive functioning, occurrence of specific adverse events, and withdrawals.

Cognitive functioning. For studies on cognitive functioning, some evidence suggests no differences in changes in cognitive functioning between groups, while some evidence suggests electroconvulsive therapy may have a deleterious impact on cognitive functioning compared to repetitive transcranial magnetic stimulation (insufficient strength of evidence). No differences between groups on a single-item measure of cognitive functioning were found in a study comparing electroconvulsive therapy with electroconvulsive therapy and repetitive transcranial magnetic stimulation (insufficient strength of evidence).

Specific adverse events. One study comparing electroconvulsive therapy with a combination of electroconvulsive therapy and repetitive transcranial magnetic stimulation found no differences in specific adverse events (low strength of evidence).

Withdrawals. A single study with a small sample size indicated no difference in withdrawals due to adverse events for the electroconvulsive therapy group when compared to repetitive transcranial magnetic stimulation but did not report on the significance of this result (low strength of evidence). Evidence for electroconvulsive therapy compared with repetitive transcranial magnetic stimulation indicated higher rates of overall withdrawals in the electroconvulsive therapy compared to the repetitive transcranial magnetic stimulation group (low strength of evidence).

Indirect evidence.
Cognitive functioning. Mixed evidence on cognitive functioning in repetitive transcranial magnetic stimulation versus sham was insufficient evidence to draw a conclusion (insufficient strength of evidence).

Specific adverse events. Repetitive transcranial magnetic stimulation groups reported significantly more scalp pain at the stimulation site (low strength of evidence). Some differences in the frequency of specific adverse events were seen when comparing vagus nerve stimulation and sham groups, but the significance of the findings was not reported (low strength of evidence).

Withdrawals. Findings were mixed as to whether repetitive transcranial magnetic stimulation groups had greater rates of withdrawals (overall and due to adverse events) than groups receiving sham procedures (insufficient evidence for both). Withdrawals attributable to adverse events were higher in the vagus nerve stimulation group compared with sham (low strength of evidence). No studies reported on withdrawals for cognitive behavioral / interpersonal psychotherapy groups versus those receiving some form of usual care.

Efficacy or Harms of Nonpharmacologic Treatments for Selected Patient Subgroups

Direct evidence. No studies were identified that directly compared nonpharmacologic interventions in selected populations, such as the elderly, those with stroke, or those with other medical comorbidities.

Indirect evidence. Two trials compared repetitive transcranial magnetic stimulation with sham. All findings provided low strength of evidence. For young adults (ages 18–37), one trial found that repetitive transcranial magnetic stimulation produced a greater decrease in depressive severity and a greater response rate than sham. A second trial, conducted in older adults with post-stroke depression, found that repetitive transcranial magnetic stimulation produced a greater decrease in depressive severity and a greater response rate but no difference in remission rates compared with a sham control.

Health-Related Outcomes of Nonpharmacologic Treatments

Direct evidence. The focus of patient-reported health-related outcomes in this report was quality of life (various measures) and ability to function in daily life. One study compared electroconvulsive therapy with a combination of electroconvulsive therapy and repetitive transcranial magnetic stimulation and found no differences between groups in improvement on the Global Assessment of Functioning scale (low strength of evidence).

Indirect evidence. Two trials (both in mixed major depressive disorder/bipolar populations) assessed general health status and mental and physical functioning (all health domains related to quality of life). In one fair trial, low repetitive transcranial magnetic stimulation had significantly greater improvement in health status and daily functioning than sham, while this relationship approached statistical significance when comparing high repetitive transcranial magnetic stimulation to sham (as measured by the Global Assessment of Functioning scale; low strength of evidence). In the other fair trial, vagus nerve stimulation and sham groups did not differ significantly in daily functioning (as measured by the 36-item Medical Outcomes Study Short Form [MOS SF-36]; low strength of evidence). No studies of psychotherapy were identified.

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Trivedi 2009
This systematic review included five unique RCTs comparing medications to psychotherapy in patients with major depressive disorder who have not responded to initial treatment with antidepressants. One trial had both “substitution with psychotherapy” and “augmentation with psychotherapy” arms, therefore it was treated as two different studies, resulting in a total of six studies evaluating 567 patients. Psychotherapy was examined as an augmentation to antidepressant medication in four studies and as a substitution treatment to replace medication in two studies.

Two good quality, moderate-sized trials showed equal benefit from augmenting antidepressant medication with cognitive therapy and from active medication management, one fair quality small study showed lithium augmentation to be more beneficial than cognitive therapy, and one fair quality trial showed short-term benefit from augmentation through 16 sessions of dialectic behavior therapy. A moderate-sized, good quality study and a small, poor quality study found equal benefit from substituting cognitive therapy for antidepressant treatment and from continuing management of depression with medication. In conclusion, current trials do not support favoring psychotherapy over antidepressant medication for mid-life adults with treatment resistant MDD; however, psychotherapy appears to be an equally effective treatment compared to antidepressant medication and is therefore a reasonable treatment option for this demographic.

[Evidence Source]

Overall Summary

Repetitive transcranial magnetic stimulation is beneficial for all three depression outcomes (severity of depressive symptoms, response rate, remission rate) compared to placebo, but vagus nerve stimulation is not. While there are no placebo controlled trials of electroconvulsive therapy, it produces a significantly greater decrease in depression severity and better response rates than medications. When comparing electroconvulsive therapy to repetitive transcranial magnetic stimulation, there are no differences in terms of depression severity, response rates, and remission rates. There is little difference between interventions in safety profiles, with the exception of electroconvulsive therapy compared with repetitive transcranial magnetic stimulation, for which there are higher rates of overall withdrawals in the electroconvulsive therapy compared to the repetitive transcranial magnetic stimulation group. When compared to placebo, repetitive transcranial magnetic stimulation had significantly more scalp pain at the stimulation site, and the vagus nerve stimulation group had more withdrawals attributable to adverse events compared with sham. There were no eligible studies identified that evaluated psychotherapy for patients who had failed two different trials of antidepressants. For patients who have not responded to initial treatment with antidepressants, psychotherapy appears to be an equally effective treatment compared to antidepressant medication and is therefore a reasonable treatment option.

PROCEDURES

Electroconvulsive therapy

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Repetitive transcranial magnetic stimulation
Vagus nerve stimulation
Cognitive behavioral therapy or interpersonal psychotherapy

DIAGNOSES

Major depressive disorder

APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
296.2	Major depressive disorder single episode
296.20	Major depressive affective disorder, single episode, unspecified
296.21	Major depressive affective disorder, single episode, mild
296.22	Major depressive affective disorder, single episode, moderate
296.23	Major depressive affective disorder, single episode, severe, without mention of psychotic behavior
296.24	Major depressive affective disorder, single episode, severe, specified as with psychotic behavior
296.25	Major depressive affective disorder, single episode, in partial or unspecified remission
296.26	Major depressive affective disorder, single episode, in full remission
296.3	Major depressive disorder recurrent episode
296.30	Major depressive affective disorder, recurrent episode, unspecified
296.31	Major depressive affective disorder, recurrent episode, mild
296.32	Major depressive affective disorder, recurrent episode, moderate
296.33	Major depressive affective disorder, recurrent episode, severe, without mention of psychotic behavior
296.34	Major depressive affective disorder, recurrent episode, severe, specified as with psychotic behavior
296.35	Major depressive affective disorder, recurrent episode, in partial or unspecified remission
296.36	Major depressive affective disorder, recurrent episode, in full remission
296.82	Atypical depressive disorder
ICD-9 Volume 3 (Procedure Codes)	
94.27	Other Electroshock Therapy
CPT Codes	
64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
64568	Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
64569	Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
64570	Removal of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
90804	Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an office or outpatient facility, approximately 20 to 30 minutes face-to-face with the patient

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CODES	DESCRIPTION
90805	with medical evaluation and management services
90806	Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an office or outpatient facility, approximately 45 to 50 minutes face-to-face with the patient
90807	with medical evaluation and management services
90808	Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an office or outpatient facility, approximately 75 to 80 minutes face-to-face the patient
90809	with medical evaluation and management services
90816	Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an inpatient hospital, partial hospital or residential care setting, approximately 20 to 30 minutes face-to-face with the patient
90817	with medical evaluation and management services
90818	Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an inpatient hospital, partial hospital or residential care setting, approximately 45 to 50 minutes face-to-face with the patient
90819	with medical evaluation and management services
90821	Individual psychotherapy, insight oriented, behavior modifying and/or supportive, in an inpatient hospital, partial hospital or residential care setting, approximately 75 to 80 minutes face-to-face with the patient
90822	with medical evaluation and management services
90867	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
90868	Subsequent delivery and management, per session
90870	Electroconvulsive therapy (includes necessary monitoring)
95970	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (ie, cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/ transmitter, without reprogramming
95974	Complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, first hour
95975	Complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, each additional 30 minutes after first hour
HCPCS Codes	
None	

Note: Inclusion on this list does not guarantee coverage

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

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