**Final Key Questions and Background**

**Nonpharmacologic Treatments for Treatment-Resistant Depression**

**Introduction**

According to a national U.S. survey conducted between 2001 and 2003, 16.6% of adults will experience a major depressive disorder (MDD) in their lifetime. Failure to respond to initial treatment plans involving psychotherapy and/or an antidepressant medication is common. Treatment-resistant depression, or TRD, is a term used to describe MDD that does not respond to initial treatment with antidepressant medication, which is considered appropriate for moderate to severe MDD. A large multicenter study (STAR*D) found that approximately one third of MDD patients achieved remission with an initial antidepressant and approximately half achieved remission after a second antidepressant trial, provided the patients remained in treatment. Although a standard definition of TRD is not recognized, a recent evidence report prepared for the Agency for Healthcare Research and Quality (AHRQ) concluded that there is an emerging consensus that failure of ≥ 2 prior adequate pharmacologic trials is an appropriate definition. Treatment resistance may also occur in depression related to bipolar disorder.

Nonpharmacologic treatments are often tried when pharmacotherapy has failed or has proved intolerable to a patient. Such options include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), transcranial direct current stimulation (tDCS), and vagus nerve stimulation (VNS).

The Centers for Medicaid & Medicare Services has no national policy on ECT, TMS, DBS, or tDCS. The FDA has approved ECT for depression and has approved TMS and VNS specifically for TRD. The FDA has not approved DBS or tDCS for depression.

**Policy Context**

Nonpharmacologic treatments for depression that does not respond to first line treatments was selected for review based on concerns about the safety, efficacy and cost of the treatments. Depression is relatively common among adults and contributes to or is associated with higher rates of other disease processes, disability and reduced quality of life. This review will help to identify safe and effective evidenced-based care for TRD.

**Scope of this HTA**

VNS will not be covered in this report. Washington HTA previously reviewed VNS in 2009 (Vagus Nerve Stimulation for Depression and Epilepsy). An updated search for new literature conducted in August 2013 revealed no new evidence likely to change the conclusions of the 2009 report.

**Population:** Adults with major depressive disorder or bipolar depression who have not responded to prior adequate pharmacologic treatments.
Interventions: Nonpharmacologic treatments for depression, including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS).

Comparators: Sham treatment, treatment as usual, other nonpharmacologic treatment (including psychotherapy as a new treatment in response to treatment failure), pharmacologic treatment (a new medication to be tried in response to treatment failure), or combination therapy that does not include the nonpharmacologic therapy of interest.

Outcomes: Response, remission, depression severity, functional status, quality of life (QOL)

**Final Key Questions**

1. a. Are the following nonpharmacologic treatments effective for TRD?
   - Electroconvulsive therapy (ECT)
   - Repetitive transcranial magnetic stimulation (rTMS)
   - Transcranial direct current stimulation (tDCS)
   - Deep brain stimulation (DBS)

   b. Does the effectiveness of these treatments vary according to treatment intensity, duration of treatment, use in an augmentation versus switch strategy, or any other variation in the manner in which TRD treatment was administered?

2. What adverse effects are associated with nonpharmacologic treatments for TRD and what are the rates of withdrawal due to lack of benefit?

3. Does the effectiveness of nonpharmacologic treatments for TRD vary by subpopulation defined by such factors as: age, race/ethnicity, gender, disease severity, disease duration, depression diagnosis (unipolar or bipolar depression), symptom type (e.g., psychotic, postpartum), comorbidities, or number and type of prior treatments (including other nonpharmacologic treatments)?

4. What are the cost implications and cost-effectiveness of nonpharmacologic therapies for TRD?

**Public Comment & Response**

See [Draft Key Questions: Public Comment and Response](#) document published separately.