Effective Health Care Program

Mental Health
Depression

Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults

Focus of Research for Clinicians

In response to a request from the public, a systematic review of 63 clinical studies published between January 1980 and November 2010 examined the comparative effectiveness, benefits, and adverse effects of nonpharmacologic interventions for treatment-resistant depression (TRD) in adults. The full report, listing all studies, is available at www.effectivehealthcare.ahrq.gov/trd.cfm. This summary, based on the full report of research evidence, is provided to inform discussions of options with patients and to assist in decisionmaking along with consideration of a patient's values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

Among patients who receive appropriate treatment for major depressive disorder, about 50 percent will not adequately respond. Patients who do not respond to at least two adequate antidepressant trials are considered to have TRD for the purpose of this report.

Patients with TRD are significantly less likely to respond to subsequent medications and thus may require nonpharmacologic treatments, which have traditionally included electroconvulsive therapy (ECT) and psychotherapies such as cognitive behavioral therapy (CBT) and interpersonal therapy (IPT). Newer nonpharmacologic approaches for major depressive disorder have broadened potential options to include repetitive transcranial magnetic stimulation (rTMS) and vagus nerve stimulation (VNS). Descriptions of these treatments are available on page 2.

Current evidence indicates that ECT has a role in the treatment of people with depression and in certain subgroups. The current role for ECT in depression is for treatment resistance or intolerance and for suicidality. Recently, trials have focused on the newer treatments rTMS and VNS. The systematic review focused on the effectiveness of the various nonpharmacologic options compared with each other and with pharmacotherapy, and also evaluated the efficacy of rTMS and VNS.

Conclusion

Comparative clinical research on nonpharmacologic treatments for TRD is in its infancy. Few direct comparisons between nonpharmacologic options were available, and all available evidence involving direct comparisons was either insufficient or of low strength. Within this limited evidence base, comparative outcomes for both ECT and rTMS are similar, with no apparent synergistic effect from combining these therapies. Evidence suggests that rTMS is effective in reducing depressive severity and producing response and remission over sham treatment. The effectiveness of ECT was not addressed in the review. No benefit was seen for VNS over sham treatment. Evidence regarding adverse effects is limited.

Clinical Bottom Line

Comparative Effectiveness of ECT Versus Pharmacotherapy

ECT, when compared with paroxetine, produced a greater improvement in depressive severity (9 points on the HAM-D, $p = 0.001$) and treatment response rate (71.4% for ECT vs. 27.8% for paroxetine, $p = 0.006$). ●○○

- No other studies evaluating other pharmacotherapies were included in the systematic review, and the adverse event rates of ECT versus pharmacotherapy were not compared in studies.

Comparative Effectiveness of rTMS ± ECT Versus ECT Alone

rTMS does not clearly differ from ECT with respect to depressive severity, response rates, and remission rates. Available evidence showed that ECT and rTMS groups may not differ with respect to withdrawals due to adverse events, but overall withdrawal rates were lower with rTMS than with ECT. ●○○

- Evidence is insufficient to evaluate ECT versus rTMS with respect to adverse events and effects on cognitive or daily functioning. ○○○

  Treatment interventions combining ECT with rTMS do not clearly differ from treatment with ECT alone with respect to depressive severity, remission rates, improvements to daily functioning, or specific adverse events. ●○○

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Strength of Evidence Scale

High:	●●●	Further research is very unlikely to change the confidence in the estimate of effect.
Moderate:	●●○	Further research may change the confidence in the estimate of effect and may change the estimate.
Low:	●○○	Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient:	○○○	Research is either unavailable or does not permit estimation of a treatment effect.

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Effectiveness and Adverse Effects of VNS*

VNS does not clearly differ from sham treatment with respect to improvements in depressive severity, response rates, or daily functioning. However, VNS may produce increased rates of some specific adverse effects (see Table 2) and may have greater withdrawals attributed to adverse events. ●○○

Effectiveness and Adverse Effects of rTMS*

Benefits (rTMS vs. sham treatment)

- Greater decrease in depressive severity (5+ points on the HAM-D). ●●●
- Three times as likely to produce a response (number needed to treat = 5). ●●●
- Six times as likely to achieve remission of depressive symptoms (number needed to treat = 4). ●●○
- Better outcome for depressive severity and response rates for young adults. ●○○
- Better outcome for depressive severity in older adults with poststroke depression than with sham treatment. ●○○
- Greater improvement in health status and daily functioning. ●○○
- Evidence is insufficient to evaluate the ability of rTMS to maintain response or remission. ○○○

Adverse Effects (rTMS vs. sham treatment)

- More scalp pain at the stimulation site. ●○○
- Evidence is insufficient to permit conclusions for withdrawals due to adverse events or patient nonadherence. ○○○

Other Comparisons

Evidence is insufficient to evaluate the comparative effectiveness or adverse effects between the following comparators:

- ECT versus sham treatment. ○○○
- rTMS + pharmacotherapy versus pharmacotherapy alone or sham treatment alone. ○○○
- Psychotherapy versus control treatment or pharmacotherapy. ○○○

These results do not suggest that ECT and psychotherapy are ineffective treatments for TRD but merely that data are lacking for these comparisons within the population requirements used for the systematic review.

*VNS and rTMS have been approved by the U.S. Food and Drug Administration (FDA) for treatment of major depressive disorder but are not yet approved for the treatment of TRD.

HAM-D = Hamilton Depression Rating Scale

Table 1: Descriptions of Nonpharmacologic Treatments Studied

Intervention	Description
Electroconvulsive Therapy (ECT)	Passing an electric current through the brain after administering anesthetic and muscle relaxants to produce a convulsion.
Repetitive Transcranial Magnetic Stimulation (rTMS)	Focal magnetic stimulation through the scalp without the use of anesthesia.
Vagus Nerve Stimulation (VNS)	Surgically implanted electrodes around the left vagus nerve to modulate mood and control seizures.
Psychotherapies (CBT or IPT)	Psychotherapy to identify negative depressogenic cognitions or interpersonal behaviors.

Table 2: General Adverse Effects Associated With Nonpharmacologic Therapies

The information below is generally reported and was not critically reviewed in the source report.

Treatment	Common adverse effects or contraindications
Electroconvulsive Therapy (ECT)	Potential risks include seizure and adverse cognitive effects, in addition to the risk of adverse effects from anesthesia. There is an increased risk of complications in patients with unstable cardiac disease, ischemia, arrhythmias, hemorrhage, or increased intracranial pressure.
Repetitive Transcranial Magnetic Stimulation (rTMS)	Potential adverse effects include mild headaches, scalp pain, syncope, and transient hearing changes. Should not be used in patients with a high risk of seizure or patients who have metal objects anywhere in the body (such as cardiac pacemakers, medication pumps, and cochlear implants) except the mouth.
Vagus Nerve Stimulation (VNS)	Potential adverse effects include voice alteration, cough, neck pain, paresthesia, and dyspnea. Should not be used in patients with bilateral or left cervical vagotomy. Patients with VNS implants should not receive shortwave diathermy, microwave diathermy, or ultrasound diathermy.
Cognitive Behavioral Therapy (CBT) or Interpersonal Therapy (IPT)	CBT and IPT do not have any serious risks or adverse effects associated with them. Should not be used in patients with cognitive disorders, cognitive impairment, or limited cognitive functioning.

Gaps in Knowledge

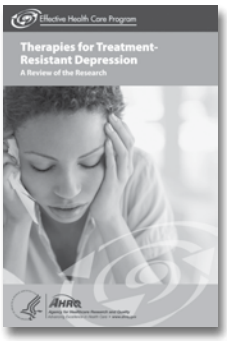
- Information about health-related outcomes that concern quality of life or levels of functional impairment is substantially missing from current studies.
- Few studies compare nonpharmacologic interventions with each other or with pharmacologic interventions. Moreover, the comparative effectiveness of combined treatment interventions has not been evaluated.
- Almost no direct evidence exists on how the comparative effectiveness of nonpharmacologic treatments might differ as a function of symptom subtypes or for subgroups defined by sociodemographic characteristics (e.g., age) or by coexisting medical conditions (e.g., depression following a stroke or a myocardial infarction; perinatal depression).
- The following shortcomings of evaluated studies may limit the applicability or generalizability of some findings:
  - Inconsistent definitions of TRD
  - Inconsistent reporting of measured outcomes
  - Short followup periods
  - Limited, short-term, variable, and inconsistent adverse event reporting

What To Discuss With Patients and Caregivers

- The definition of TRD and why it may need different forms of treatment.
- The potential benefits and adverse events associated with nonpharmacologic treatment options.
- The patient's values and preferences regarding the trade-offs between the benefits and harms of the various treatment options.
- The availability of nonpharmacologic treatment options.

Resource for Patients and Caregivers

Therapies for Treatment-Resistant Depression, A Review of the Research is a free companion to this clinician research summary for patients and caregivers. It covers:



- A description of TRD, its symptoms, and why treatment may feel frustrating.
- Descriptions of the types of treatments, how they work, and potential side effects.
- Questions to guide a discussion with you about treatment options.

Ordering Information

For electronic copies of *Therapies for Treatment-Resistant Depression, A Review of the Research*, this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/trd.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

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