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Vagus Nerve Stimulation for Resistant Depression

Adjunctive vagus nerve stimulation (VNS) improved quality of life in a large sample of patients with highly refractory depression, even in patients who did not meet the conventional definition of depression response.

Background: VNS is FDA approved as adjunctive treatment for major depression not responsive to ≥4 medications. Its effects on quality of life have not yet been examined.

Methods: Quality-of-life data were obtained from a large 5-year clinical registry of participants in a multicenter trial. All patients received treatment as usual, which could include any combination of drugs, psychotherapy, other neurostimulation, and ECT. Adjunctive vagus nerve stimulation was offered as part of the trial. Participants were required to have failed to experience response to ≥4 antidepressants before enrollment and to commit to 5 years of follow-up. Patients were administered the Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF) and the Montgomery-Asberg Depression Rating Scale (MADRS) periodically throughout follow-up. The Q-LES-Q-SF score was reported as the percentage of the maximum possible score. The minimal clinically important difference in quality of life, defined as a ≥12% increase in the Q-LES-Q-SF percentage, is associated with a score of 1–3 (at least minimally improved) on the Clinical Global Impression–Improvement (CGI-I) scale.*

Results: The sample comprised 599 patients (417 women; mean age, 50 years): 328 who received adjunctive VNS and 271 who received only treatment as usual. About 26% of patients had a diagnosis of bipolar depression. Patients had a lifetime mean of about 8 failed antidepressant trials.

Q-LES-Q-SF scores indicated significantly better quality of life in the VNS group after 3 months, and throughout follow-up. VNS was associated with a 4-point higher average percent maximum score on the Q-LES-Q-SF throughout the range of MADRS scores. The trend was observed in both unipolar and bipolar depression, although it was not statistically significant in the latter group, with its smaller sample size.

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Patients who received VNS achieved the minimal clinically important difference in the Q-LES-Q-SF when the MADRS decrease from baseline was ≥34%—lower than the 50% decrease in symptoms typically used to define antidepressant response. The treatment-as-usual group achieved the minimal clinically important difference at average MADRS decreases of ≥56%. For a given MADRS change, patients who received VNS also had a significantly higher probability of achieving a CGI-I response—i.e., a score of 1 or 2 (odds ratio,* 2.78). Adjunctive VNS produced significantly greater improvement than treatment as usual in 8 of the 14 Q-LES-Q-SF domains of: mood, household activities, leisure activity, ability to function, overall well-being, social relationships, family relationship, and sex drive. Treatment as usual was associated with larger improvement in the economic status domain. The physical health, work, living/housing, ability to get around, and ability to work domains did not differ between the groups.

Conway C, Kumar A, Xiong W, Bunker M, et al: Chronic vagus nerve stimulation significantly improves quality of life in treatment-resistant major depression. *Journal of Clinical Psychiatry* 2018;79 (September/October):52–59. doi 10.4088/JCP.18m12178. From Washington University School of Medicine in St. Louis, MO. **Funded by Cyberonics, Inc., Houston, TX. Five of 6 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

***See Reference Guide.**

Minimum Panel for Pharmacogenetic Testing

Based on evidence-supported associations and other data, a minimum standard genetic panel has been proposed for pharmacogenetic testing in psychiatry. The recommended panel includes 5 genes with 16 variant alleles that influence metabolism of psychotropic drugs. Information from this testing can be used, in combination with clinical information, to guide medication selection and dosing.

Background: Lack of standardization of genetic test panels has been an important obstacle to translating pharmacogenetics into standard medical practice. Assays and reporting are becoming more uniform, but the gene and allele content of the assays remains to be standardized.

Methods: Data were extracted from multiple pharmacogenetics information hubs regarding 91 psychotropic drugs. In order to assemble a minimum panel of genes and alleles relevant to drugs used in psychiatry, gene-drug pairings with the highest level of evidence of a clinically relevant functional effect were identified. Included alleles were also required to have a frequency of ≥1% in 2 or more of the 7 major world ethnic groups.

Results: The authors identified 448 unique gene-drug interactions, of which 31 met criteria for inclusion; most failed to meet the required level of evidence. The majority of these interactions involved 2 cytochrome P450 enzymes, CYP2D6 and CYP2C19. Also included were CYP2C9 and HLA-A and -B genes. (See table.)

CYP2C19 is important in the metabolism of several SSRIs and tricyclic antidepressants. There are multiple nonfunctional alleles, requiring a 50% reduction of the starting dose of these antidepressants, and 2 increased-function alleles, identifying patients who are unlikely to benefit from the affected antidepressants. The proposed panel includes 2 nonfunctional alleles and 1 increased-function allele. The other relevant alleles are too uncommon to recommend testing.

Proposed Minimum Pharmacogenetic Testing Panel

Gene	Alleles
CYP2C9	*2, *3
CYP2C19	*2, *3, *17
CYP2D6	*3, *4, *5, *6, *10, *17, *41, *1xN, *2xN
HLA-A	*31:01
HLA-B	*15:02

CYP2D6 is involved in the metabolism of all tricyclic antidepressants, most SSRIs, and about half of antipsychotics. Available pharmacogenetic testing panels include a highly inconsistent representation of the alleles of this complex gene. The recommended minimum panel includes 4 no-function alleles of CYP2D6, 3 decreased-function alleles, and 2 increased-function alleles.

CYP2C9 is involved in the metabolism of several drugs, but only 1, phenytoin, is likely to be encountered in psychiatry. The panel includes 2 alleles that decrease phenytoin metabolism. Treatment guidelines recommend a 25% dose decrease if 1 of these alleles is present and a 50% decrease if both are present.

There are >9000 HLA-A and HLA-B alleles, but only 2 are recommended for the panel. Both alleles are associated with severe cutaneous adverse reactions following the use of aromatic anticonvulsants, such as carbamazepine, oxcarbazepine, and phenytoin. The severity of these reactions has led the FDA and Health Canada to recommend genetic testing before prescribing, particularly for people of Chinese and Southeast Asian descent. Several other HLA alleles have also been associated with these reactions and may be included in future panels.

Discussion: The proposed panel is based on currently available evidence and will require regular updates as the evidence base grows. There is also no consensus on which patients will require pharmacogenetic testing or when. However, it will likely be most useful for patients experiencing a high adverse-effect burden or who have not benefitted from previous medication. The authors also note that prescribing decisions should not be based solely on pharmacogenetic testing, which is intended to be used as a companion decision support tool for more precise selection and dosing of medications.

Bousman C, Maruf A, Müller D: Towards the integration of pharmacogenetics in psychiatry: a minimum, evidence-based genetic testing panel. *Current Opinion in Psychiatry* 2018; doi 10.1097/YCO.0000000000000465. From the University of Calgary, Canada; and other institutions. **This review was conducted without external funding. Two of 3 study authors disclosed potentially relevant relationships.**

Common Drug Trade Names*: carbamazepine—*Tegretol*; oxcarbazepine—*Trileptal*; phenytoin—*Dilantin

Personal Pharmacogenetic Testing Approved

The 23andMe Personal Genome Service Pharmacogenetic Reports test has gained FDA approval for direct-to-consumer sale.[1] The test provides information about genetic variants that may be related to patients' ability to metabolize certain medications. The FDA cautions that these test results do not determine which medications are appropriate for a patient, provide medical advice, or diagnose any health conditions. Rather, the results should be used to help inform discussions with the patient's healthcare provider.

In a separate news release, the FDA cautions that some genetic tests claim to predict how a person will respond to specific medications.[2] However, these claims have not been reviewed by the FDA and may not be backed by sufficient scientific or clinical evidence. They warn that changing treatment based on the results of these tests could lead to inappropriate treatment decisions and potentially serious health consequences. The agency acknowledges that there are a limited number of cases for which at least some evidence supports a correlation between a genetic variant and drug levels. However, in these cases, the evidence is described in the labeling for approved genetic tests and medications.

[1]FDA News Release: FDA allows marketing of first direct-to-consumer tests that provide genetic risk information for certain conditions.
Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm.

[2]FDA Drug Safety Communication: The FDA warns against the use of many genetic tests with unapproved claims to predict patient response to specific medications.
Available at https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm624725.htm.

Low-Level Light Therapy for Depression

Photobiomodulation (PBM) is a promising experimental treatment for major depressive disorder, according to a systematic literature review. The treatment—also called low-level light therapy, low-level laser therapy, or near-infrared light therapy—is a device-based treatment that involves exposing the scalp or peripheral tissues to a restricted wavelength of light. It differs from bright light therapy by not involving the retina and not using a broad spectrum of visible light. Potential advantages of PBM over other device-based therapies are low cost and the feasibility and safety of at-home administration. Modest evidence of its antidepressant effects is available from animal experiments and a few preliminary clinical studies.

The biological effects of infrared or near-infrared (NIR) light are mechanistically different from other wavelengths and are based on their ability to penetrate the tissues and act on a specific mitochondrial chromophore, or light-absorbing region, the cytochrome C oxidase. Irradiation is delivered by low-level lasers or light-emitting diodes. Therapeutic PBM has been used to treat such conditions as muscle pain, wounds, neuropathic pain, and headache. When delivered to the scalp, NIR can penetrate to a depth of about 2 cm, reaching target areas of the brain at an adequate energy density.

Depression is associated with brain hypometabolism and mitochondrial dysfunction. In animal studies, PBM was shown to increase mitochondrial activity. It may also prevent oxidative stress and inflammation, improve neuroplasticity, stimulate neurogenesis, and protect against cell death. In healthy human subjects, transcranial PBM increased cerebral oxygenation and blood flow.

Transcranial PBM—the delivery method used in all animal studies—had positive effects on depression-related behaviors. The evidence of antidepressant efficacy in humans is inconclusive. There have been 10 studies in humans, most using transcranial delivery. Other modalities include transcutaneous delivery, including transcutaneous treatment of acupuncture points, and intravenous PBM. Study designs have been weak, and stimulation parameters have differed among studies, making it difficult to combine results. The antidepressant effects are generally positive, but the effects of a single session are transient and multiple treatments will likely be required. A single treatment with PBM appears to be safe, but there are no data on the safety of multiple sessions. A lack of information on optimal dosimetry is the biggest challenge to future research.

Caldieraro M, Cassano P: Transcranial and systemic photobiomodulation for major depressive disorder: a systematic review of efficacy, tolerability and biological mechanisms. *Journal of Affective Disorders* 2019;243:262–273. doi 10.1016/j.jad.2018.09.048. From the Hospital de Clinicas de Porto Alegre Brazil; and Massachusetts General Hospital, Boston. **This review was conducted without specific funding. One study author disclosed potentially relevant financial relationships; the other author declared no competing interests.**

Cortisol and Response to Psychological Therapies

Levels of cortisol in hair samples were predictive of response to psychological therapy for depression and anxiety. It remains to be determined which types of therapy are affected by pretreatment alterations in the HPA axis.

Methods: The study was conducted in patients referred for treatment of unipolar or bipolar depression or anxiety disorders, including PTSD. Participants had to provide hair samples of ≥3 cm, reflecting 3 months of growth. Childhood trauma, another outcome variable of interest, was assessed using the Childhood Trauma Questionnaire, which measures the

domains of emotional, physical, and sexual abuse and emotional and physical neglect. Patients received treatment according to recommendations of the U.K.'s National Institute for Health and Care Excellence. Depending on severity, they received either step 2 interventions (usually ≤6 sessions of guided self-help or computerized cognitive behavioral therapy [CBT] and group therapies such as behavioral activation and mindfulness) or level 3 therapies (usually longer, high-intensity CBT). Depression response was defined as a decrease of ≥6 points on the Patient Health Questionnaire–9 depression module, and anxiety response as a ≥5-point decrease on the Generalized Anxiety Disorder Scale–7. Because it is assumed that early parental behavior toward offspring can affect HPA-axis reactivity, childhood trauma was also assessed as a potential predictor of response.

Results: Most of the 89 study subjects were women (n=83), in part because of their increased ability to give hair samples. The most frequent diagnoses were generalized anxiety disorder (61% of patients), major depressive disorder (42%), and agoraphobia (38%). About half of the sample received low-intensity therapies. Overall, 43% of patients achieved depression response and 52% achieved anxiety response. Patients whose depression did not respond to psychological therapy were found to have significantly lower pretreatment hair cortisol levels than responders (132 vs 153 pg/mg; p=0.041). Similarly, those whose anxiety was nonresponsive had lower hair cortisol levels than responders (132 vs 151 pg/mg), but the difference did not reach significance.

One-fourth of the study subjects had experienced childhood trauma of any type. Depression nonresponse was associated with higher frequencies of physical and sexual abuse and overall childhood trauma. Anxiety nonresponse was associated with more emotional and physical abuse and overall trauma. However, hair cortisol levels were not correlated with childhood trauma.

Discussion: The relationship of HPA activation with treatment response is complex. In some previous research, higher rather than lower cortisol concentrations predicted nonresponse to therapy. The difference may reflect the timing of the measurement or the fact that the present study group was diagnostically mixed and highly comorbid. Lower pretreatment cortisol in patients with anxiety may be linked with failure to mount a cortisol response during treatment. These results require replication in studies stratified by diagnosis as well as presence or absence of childhood trauma.

Fischer S, King S, Papadopoulos A, Hotopf M, et al: Hair cortisol and childhood trauma predict psychological therapy response in depression and anxiety disorders. *Acta Psychiatrica Scandinavica* 2018;138:526–535. doi 10.1111/acps.12970. From King's College London, U.K.; and other institutions. **Funded by the Swiss National Science Foundation; and other sources. The authors declared no competing interests.**

Virtual Reality Exposure Therapy for Anxiety

According to a meta-analysis, virtual reality exposure therapy (VRET) is an effective treatment for anxiety and related disorders, with effects similar to in-vivo exposure.[1]

Methods: Randomized or quasi-randomized controlled trials of VRET for anxiety disorders were identified in the literature. The search found 30 trials, including 13 that had been covered in an earlier meta-analysis by these authors.[2] The total sample size was 1057, and patients' diagnoses included specific phobia, social anxiety disorder, performance anxiety, PTSD, and panic disorder with or without agoraphobia. Control treatments included wait-lists, psychological controls such as relaxation or attention control, and in-vivo exposure. Study outcome measures were: disorder-specific subjective distress, as well as behavioral, cognitive, psychophysiological, and general subjective distress.

Results: Compared with waitlist and psychological control conditions, VRET was more effective at reducing disorder-specific distress (effect size [ES],* 0.88), as well as behavioral (ES, 0.87), cognitive (ES, 1.15), and psychophysiological (ES, 064) outcomes, and general subjective distress (ES, 0.49). These results were maintained over various durations of follow-up.

Analysis of specific diagnoses yielded effect sizes of 1.03 for panic disorder, 0.97 for social anxiety disorder and performance anxiety combined, 0.95 for specific phobias, and 0.59 for PTSD. When VRET was compared with in-vivo exposure, the 2 treatments' effects on outcomes were similar or slightly favored in-vivo exposure overall and across the specific anxiety diagnoses.

Discussion: In addition to its potential to extend access of exposure-based cognitive behavioral therapy via lower cost, surveys indicate that many people with anxiety disorder would prefer VRET to traditional in-vivo exposure therapy.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis; however, the source of funding was not included.

[1]Carl E, Stein A, Levihn-Coon A, Pogue J, et al: Virtual reality exposure therapy for anxiety and related disorders: a meta-analysis of randomized controlled trials. *Journal of Anxiety Disorders* 2018; doi 10.1016/j.janxdis.2018.08.003. From the University of Texas at Austin; and other institutions. **Source of funding not stated. One of 9 study authors disclosed potentially relevant financial relationships.**

[2]Powers M, Emmelkamp P: Virtual reality exposure therapy for anxiety disorders: a meta-analysis. *Journal of Anxiety Disorders* 2008;22:561–569.

***See Reference Guide.**

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Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ).