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TMS Modalities Compared for Depression

There appears to be little difference in efficacy or acceptability between available transcranial magnetic stimulation modalities in patients with depression. However, there may be small advantages for bilateral repetitive transcranial magnetic stimulation (rTMS) and possibly priming low-frequency rTMS, according to a network meta-analysis comparing 8 different approaches.

Methods: The analysis included published randomized clinical trials comparing TMS interventions, including sham TMS, in patients with a primary diagnosis of an acute unipolar or bipolar depressive episode. The primary efficacy outcome of the analysis was response, defined as a ≥50% reduction in symptoms measured by each study's primary outcome scale or by the 17-item Hamilton Rating Scale for Depression (HAMD-17) if the study did not specify a scale. Acceptability, the other primary outcome, was measured as the rate of treatment discontinuation. Remission, a secondary outcome, was defined as a score of ≤7 on the HAMD-17, ≤8 on the 21-item HAM-D, or ≤10 on the Montgomery-Asberg Depression Rating Scale.

Results: A total of 81 studies were included in the analysis, some with multiple active treatment arms. The studies included >4200 patients and 101 comparisons of 8 different active brain-stimulation treatments and sham TMS. The most frequent comparison was high-frequency rTMS versus sham. Most trials included only patients with treatment-resistant disease, applied TMS as an add-on therapy, and comprised 10–15 TMS sessions.

According to the network meta-analysis, 5 forms of TMS were significantly superior to sham treatment. (See table, next page.) Generally, the newer modalities (e.g., accelerated, deep [H-coil], and synchronized TMS) were not superior to sham treatment. Bilateral rTMS was superior to synchronized TMS, but no other difference emerged among active treatments. Estimates of relative efficacy in producing remission were similar to response. The rankings for relative acceptability were parallel to the response ranking, although all active

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treatments had equivalent acceptability to sham TMS. Priming TMS and bilateral rTMS had the optimal combination of efficacy and acceptability.

Relative odds of response from network meta-analysis of rTMS modalities		
Superior Treatment	**Comparator**	**Odds Ratio* for Response**
Priming TMS	Sham	4.37
Bilateral rTMS	Sham	4.22
High-frequency rTMS	Sham	2.73
Theta-burst stimulation	Sham	3.37
Low-frequency rTMS	Sham	2.70
Bilateral rTMS	Synchronized TMS	3.65

Discussion: The study authors caution that the findings for most comparisons are imprecise, in part because of a small number of studies investigating modalities other than bilateral, high-frequency, and low-frequency rTMS. The positive results for priming TMS and theta-burst stimulation are based on only a few studies and require further investigation.

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

Brunoni A, Chaimani A, Moffa A, Razza L, et al: Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.3644. From the University of Sao Paulo, Brazil; and other institutions. **Source of funding not stated. One study author disclosed financial relationships with commercial sources; 2 authors disclosed relationships with noncommercial sources; and the 4 authors declared no competing interests.**

***See Reference Guide.**

Twice-Daily rTMS for Resistant Depression

In a randomized trial, twice-daily repetitive transcranial magnetic stimulation was superior to once-daily rTMS in patients with treatment-resistant depression.

Methods: Study participants were right-handed patients with nonpsychotic major depression, refractory to ≥2 adequate trials of antidepressants from 2 classes, and naive to TMS. They were encouraged to stop taking their antidepressant, although this was not always possible. Patients were randomly assigned to once- or twice-daily rTMS or to once- or twice-daily sham stimulation and received treatment on 15 consecutive weekdays (starting Monday) for 3 weeks. The first session was at 8 AM, and those receiving a second treatment returned to the clinic at about 5 PM. Electrode placement over the left prefrontal cortex was confirmed by structural MRI. High-frequency (20 Hz) rTMS was delivered in sessions of approximately 40 trains (2 sec each) at 100% resting motor threshold, with an intertrain interval of 1 minute. Patients received 1600 pulses per session, for a total of 24,000 or 48,000 pulses. Outcome measures were the 17-item Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impression–Severity (CGI-S) scale.*

Results: A total of 98 patients were randomized and started rTMS; 89 completed the 3-week treatment and additional 2-week follow-up. At the end of treatment, HAM-D scores were significantly lower for single-session rTMS than in the 2 sham groups, and significantly lower for twice-daily rTMS than once-daily rTMS. (See table.) For the CGI-S score, only twice-daily rTMS had significantly better results than the other treatments. Results at 5 weeks did not differ

statistically from results at 3 weeks. Active rTMS was associated with higher rates of response and remission than sham treatment. Likelihood of remission in patients receiving active rTMS was significantly associated with baseline HAM-D scores and with the number of sessions per day. Concurrent antidepressant medication was associated with a higher likelihood of response to rTMS.

Change from Baseline to Week 3				
	rTMS		Sham	
	Once Daily	Twice Daily	Once Daily	Twice Daily
HAM-D Baseline	30.6	29.7	29.4	30.3
HAM-D Week 3	15.6	13.1	25.4	27.0
CGI-S Baseline	4.8	4.5	4.8	5.0
CGI-S Week 3	2.6	2.1	4.2	4.4
	rTMS Groups Combined		Sham Groups Combined	
HAM-D Response†	29 (59%)		1 (2.5%)	
HAM-D Remission††	12 (24.5%)		0	
CGI Response‡	49 (100%)		5 (12.5%)	
CGI Remission‡‡	25 (51%)		1 (2.5%)	

†≥50% decrease from baseline; †† Score <8; ‡ Rating of ≤3 (mildly ill or better); ‡‡ Rating of ≤2 (borderline ill or better)

Discussion: In this study, a relatively brief 3-week treatment period was chosen to optimize patient retention. Although the authors could identify no additional comparative studies of twice-daily rTMS, previous research suggests the number of pulses per day is a significant factor in inducing remission. Many patients, especially those experiencing adverse effects, may be better able to tolerate multiple sessions per day than an increased number of pulses per session. Previous research also suggests high-frequency rTMS may accelerate the response to antidepressants.

Study Rating*—18 (100%): This study met all criteria for a randomized controlled trial.

Theleritis C, Sakkas P, Paparrigopoulos T, Vitoratou S, et al: Two versus one high-frequency repetitive transcranial magnetic stimulation session per day for treatment-resistant depression: a randomized sham-controlled trial. *Journal of ECT* 2017; doi 10.1097/YCT.0000000000000387. From National and Kapodistrian University of Athens, Greece; and other institutions. **Funded by the National Alliance for Research on Schizophrenia and Depression; and other sources. The authors declared no financial relationships with commercial sources.**

***See Reference Guide.**

Cognitive Processing Therapy for PTSD

Both individual and group cognitive processing therapy (CPT) improved symptoms of post-traumatic stress disorder in active-duty military patients.[1] These improvements, which were significantly stronger with individual therapy, were maintained for ≥6 months.

Methods: Study participants were 268 active-duty U.S. Army soldiers, including 24 women, seeking treatment for PTSD after deployment to or near Iraq or Afghanistan. The study did not exclude patients taking psychotropic medication or those with substance abuse or post-concussive syndrome. Group treatment was delivered to 8–10 participants in twice-weekly, 90-minute sessions for 6 weeks. Individual therapy sessions were 60 minutes twice per week. All patients

received CPT according to a manual developed for military personnel and veterans, focusing on challenging dysfunctional cognitions and developing more balanced thinking about traumatic events via Socratic questioning. The primary outcome measures were the Posttraumatic Symptom Scale–Interview Version (PSS-I), a 17-item clinical interview that evaluates frequency and severity of PTSD symptoms, and the Posttraumatic Stress Disorder Checklist (PCL-S), a self-report measure of PTSD symptoms in the past month.

Results: According to the results of the intent-to-treat analysis,* patients receiving therapy in either format improved significantly from baseline, with effect sizes* of 1.3 and 0.7 on the PSS-I total score in the individual and group conditions, respectively (p=0.006). The percentage of patients no longer meeting PSS-I criteria for PTSD post-treatment did not differ significantly between the groups: 49% of patients who underwent individual therapy and 37% of those who underwent group therapy (number needed to treat,* 8). Effect sizes were similar for the self-reported PCL-S total score: 1.2 and 0.6, in the individual and group conditions, respectively (p=0.001). Patients receiving individual therapy improved more rapidly. At 6 months, change from baseline remained statistically significant for both forms of treatment, but between-group differences were no longer significant.

Depression, measured using the Beck Depression Inventory-II, improved significantly in both treatment arms, with effect sizes of 0.8 and 0.5 in the individual and group treatment groups, respectively. The proportion of patients with suicidality decreased by similar amounts in both groups: from 16% to 11% with individual therapy and from 19% to 9% with group therapy.

Editorial.[2] Although individual therapy performed significantly better than group therapy, this study does not suggest that group therapy for PTSD should be abandoned. Access to individual therapy is limited in many areas, and CPT is well suited to the group format, with its worksheets and highly manualized approach. Nearly 42% of trial participants did not complete the CPT protocol. Treatment retention is a substantial issue in trauma-focused therapy for PTSD, yet little research has focused on interventions to improve treatment engagement and retention.

[1]Resick P, Wachen J, Dondanville K, Pruiksma K, et al: Effect of group vs individual cognitive processing therapy in active-duty military seeking treatment for posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry* 2017;74 (January):28–36. From Duke University Medical Center, Durham, NC; and other institutions. **Funded by the US Department of Defense. The authors declared no competing interests.**

[2]Hoge C, Lee D, Castro C: Refining trauma-focused treatments for servicemembers and veterans with posttraumatic stress disorder: progress and ongoing challenges [editorial]. *JAMA Psychiatry* 2017;74 (January):13–14. From Walter Reed Army Institute of Research, Silver Spring, MD; and the University of California, Los Angeles. **The authors declared no competing interests.**

***See Reference Guide.**

Defining Treatment Resistance in Schizophrenia

Much research has been devoted to the management of treatment-resistant schizophrenia, but definitions of resistance vary widely, and treatment guidelines based on vague definitions can lead to inconsistency and delays in treatment. The Treatment Response and Resistance in Psychosis (TRRIP) working group, an international committee of expert researchers and clinicians, was convened to create a guideline for defining treatment-resistant schizophrenia.

The guideline that was developed was based on 3 key elements: a valid diagnosis of schizophrenia, specified adequacy of prior treatments, and persistence of significant symptoms despite treatment.

The consensus criteria for treatment resistance (see table, next page), diverge from most current definitions in that they require at least a moderate degree of functional impairment and in placing an emphasis on measuring treatment adherence. The recommendations also include use of clinical specifiers (e.g., treatment-resistant schizophrenia–positive symptom domain) to

better characterize patients. In addition, they recommend a lower minimum antipsychotic dosage requirement for the definition of treatment resistance. The requirements listed in the table in an abbreviated form are the minimal requirements to meet treatment-resistance criteria; the working group also specified more stringent, optimal requirements.

Consensus criteria for assessment and definition of treatment-resistant schizophrenia: Minimum requirement	
Current symptoms	
Assessment	Standardized rating scale (e.g., Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale)
Severity	At least moderate
Duration of treatment	≥12 weeks
Functioning	At least moderately impaired, using a validated scale
Adequate prior treatment	
Assessment of past response	Based on multiple sources
Duration of treatment	≥6 weeks at therapeutic dosage
Dosage	≥600 mg chlorpromazine equivalent
Number of antipsychotics	≥2 trials with different drugs
Current adherence	≥80% of prescribed dose, verified from ≥2 sources
Symptom domain subspecifiers	Positive, negative, cognitive
Time course of resistance onset	Early/medium/late (within 1, 1–5, or >5 years after treatment onset, respectively)
Ultra-treatment resistant	Above criteria, plus resistant to clozapine (*Clozaril*)

Discussion: It should be noted that the TRRIP criteria were developed to be used as a tool to aid research study design and reporting, not as a clinical treatment guideline, and clinical scenarios that could affect treatment decisions were not addressed.

Howes O, McCutcheon R, Agid O, de Bartolomeis A, et al: Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *American Journal of Psychiatry* 2016; doi 10.1176/appi.ajp.2016.16050503. From King's College London, U.K.; and other institutions. **Funded by the U.K.'s Medical Research Council; and other sources. The majority of the workgroup members (35 of 51) disclosed financial relationships with multiple commercial sources; the remaining 16 authors declared no competing interests.**

Vitamin D and Depression

In the central nervous system, a form of vitamin D (calcitrol) activates the gene expression of an enzyme(tyrosine hydroxylase) that is the rate-limiting step in the synthesis of dopamine, noradrenaline, and epinephrine, which are implicated in the pathophysiology of mood disorders. Epidemiologic studies are yielding increasing evidence that vitamin D deficiency is associated with depression. However, evidence is less clear concerning a possible therapeutic effect of vitamin D in patients with clinical depression.

Numerous cross-sectional studies have been conducted of low vitamin D status and depression, with conflicting results. Several studies reported a positive association in elderly individuals, but there is less evidence in younger patients. Three recent studies of longitudinal or mixed designs have shown associations of low vitamin D with depressive symptoms or diagnoses of clinical depression. In addition, a meta-analysis pooled data from 1 case study, 10 cross-sectional studies, and 3 longitudinal cohort studies and found a positive association between low vitamin D levels and depression.

Randomized controlled trials of vitamin D supplementation or augmentation in depression have produced conflicting results. One meta-analysis of 15 randomized trials of supplementation found that the flawed studies showed no benefit, but studies lacking serious methodologic flaws showed an improvement in depression with vitamin D supplementation. The design flaws pointed out by this author underline the need to require patients to be vitamin D deficient at baseline and to receive an adequate dose to achieve sufficiency status during the trial; such criteria were not met by many of the studies.

There have been only a few studies of augmentation of antidepressants with vitamin D. A meta-analysis of 40 worldwide clinical trials of different nutraceuticals to augment antidepressants included only 2 studies of vitamin D. These authors concluded that evidence supported the use of vitamin D to augment antidepressants.

It would seem logical that vitamin D deficiency would have a role in seasonal depression. However, cross-sectional studies have not found an association and longitudinal studies have not been conducted. A few small clinical trials have provided modest support for the benefit of vitamin D supplementation in patients with seasonal affective disorder.

Although this review does support an association between vitamin D status and depression, the direction of causality is unclear since patients with depression may isolate themselves indoors and/or change the foods they eat, both of which can affect vitamin levels.

Parker G, Brotchie H, Graham R: Vitamin D and depression. *Journal of Affective Disorders* 2017;208 (January):56–61. From the University of New South Wales and the Black Dog Institute, Sydney, Australia. **Funded by the Australian National Health and Medical Research Council. The authors declared no competing interests.**

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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–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

Intent-to-Treat Analysis (ITT): An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an ITT analysis, everyone who begins treatment is included regardless of treatment completion. ITT analyses are done to avoid the effects of crossover, drop-out, and other factors that could alter the results or inflate the magnitude of effects.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

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. The checklists are posted at www.alertpubs.com.

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Genetics and Antidepressant Response

DNA methylation may be an important epigenetic marker in predicting antidepressant response, according to a literature review. Research, although in its infancy, suggests that epigenetic modifications of several genes may be useful in individualizing antidepressant therapy.

Although associated with genetic risk, depression involves complex inheritance and has the lowest heritability of any psychiatric disorder. Several genes have been implicated in the development of depression and in antidepressant response, including brain-derived neurotrophic factor (BDNF), the serotonin transporter gene, and others. Epigenetics refers to modifications of the DNA structure that occur during the individual's life and that can alter gene expression. DNA methylation is one type of epigenetic modification. These modifications can result from exposure to pharmaceuticals, nutrition, and stress. The low heritability of major depressive disorder, variability of research findings, and high level of non-response to antidepressant drugs suggest that epigenetic mechanisms may play an important role in depression. DNA methylation is the most widely studied epigenetic modification. Medications that target epigenetic modifications are already in clinical use for cancer and neurodegenerative disorders. Many current antidepressants and mood stabilizers owe part of their therapeutic effects to altering DNA methylation of specific genes.

A literature review identified 6 published studies of epigenetic mechanisms predicting antidepressant response in major depression. Of the 6 studies, 3 examined epigenetic modification of the serotonin transporter gene SLC6A4. Results were mixed and difficult to interpret as a result of differences in study methods, assays, populations, and treatment durations. The studies had conflicting results; improvement in depression was associated with increased or decreased DNA methylation. In the only clinical study of DNA methylation of the BDNF gene, baseline methylation of a single site on the gene was predictive of poor antidepressant response. Another single study suggested that lower levels of DNA methylation of the proinflammatory cytokine interleukin-11 were associated with better response to treatment, and hypermethylation

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of different specific sites on this gene predicted response to different drugs. In the final study, levels of DNA methylation of the monoamine oxidase A gene were not predictive of antidepressant response.

Epigenetic studies in psychiatry are in their infancy, but there does appear to be preliminary evidence suggesting epigenetic involvement in antidepressant response. Although costly to conduct, long-term randomized studies appear to be warranted as their results could advance individualized medicine in psychiatry.

Lisoway A, Zai C, Tiwari A, Kennedy J: DNA methylation and clinical response to antidepressant medication in major depressive disorder: a review and recommendations. *Neuroscience Letters* 2017; doi 10.1016/j.neulet.2016.12.071. From Centre for Addiction and Mental Health, Toronto, Canada; and other institutions. **Funded by the Centre for Collaborative Drug Research; and other sources. The authors declared financial relationships with noncommercial sources.**

Mindfulness Training and Stress Response in GAD

In a randomized trial, Mindfulness-Based Stress Reduction (MBSR) was associated with favorable changes in stress hormones and inflammatory markers in patients with generalized anxiety disorder.[1] This finding suggests MBSR, a relatively inexpensive and low-stigma treatment, may decrease stress reactivity and increase resilience to stressors.

Methods: Study subjects were participants in a randomized clinical trial that showed MBSR reduced subjective ratings of stress in adults with generalized anxiety disorder.[2] This secondary analysis evaluated the effects of treatment on biological markers of stress—including cortisol and adrenocorticotropic hormone (ACTH) as markers for the effect of stress on the hypothalamic-pituitary-adrenal axis, and IL-6 and TNF-alpha as markers of acute stress inflammation. MBSR is a standardized, manualized group-based intervention, with 8 weekly sessions and an additional day-long retreat. Classes are focused on meditation, breath awareness, and gentle yoga to cultivate present moment awareness. A didactic course called Stress Management Education (SME) was designed as the control intervention, providing similar nonspecific benefits such as group interaction and therapist attention. Before and after the 8-week intervention, all patients underwent the Trier Social Stress Test, which involved public speaking and mental arithmetic in front of a judgmental panel. Blood was collected to measure biomarkers before and after the stress tests, with multiple samples obtained over about 2 hours to calculate an area under the curve.

Results: Of 79 participants in the parent study, 72 agreed to blood sample testing. Between 62 and 68 samples were available for each of the 4 biomarkers. The area under the curve for all markers decreased from baseline after 8 weeks of MBSR, while the control intervention had variable effects. The area under the curve for cortisol did not differ between the 2 groups after treatment. However, ACTH decreased in the MBSR group and increased in the SME/control group ($p=0.007$). The 2 inflammatory cytokines also decreased in the MBSR group and increased in the patients who received SME ($p=0.034$ for IL-6 and $p=0.036$ for TNF-alpha).

Discussion: These results provide additional evidence that mindfulness meditation can confer resilience to stressful events. The finding that stress markers increased after the control intervention suggests control patients may have had elevated stress in anticipation of the second test. This finding may explain the chronically high levels of stress hormones and cytokines in patients with anxiety disorders, who experience repeated stress due to their symptoms.

[1]Hoge E, Bui E, Palitz S, Schwarz N, et al: The effect of mindfulness meditation training on biological acute stress responses in generalized anxiety disorder. *Psychiatry Research* 2017; doi:10.1016/j.psychres.2017.01.006. From Massachusetts General Hospital, Boston; and other institutions. **Funded by the NIH; and other sources. Two study authors declared financial relationships with commercial sources; the remaining 6 authors declared no relevant industry relationships.**

[2]Hoge, E, et al: Randomized controlled trial of mindfulness meditation for generalized anxiety disorder: effects on anxiety and stress reactivity. *Journal of Clinical Psychiatry* 2013;74 (August):786–792. See *Psychiatry Alerts NOS* 2013;5 (September):49–50.

Neuroimaging and Depressive Subtypes

A whole-brain functional MRI (fMRI) study in a large population of patients identified 4 neurophysiological subtypes of depression. The subtypes were associated with different symptom profiles and were predictive of response to repetitive transcranial magnetic stimulation (rTMS).

Methods: The study was conducted using clinical and neuroimaging data from the international 1000 Functional Connectomes Project. Resting-state fMRI brain scans were carried out to identify areas of dysfunction and abnormal connectivity in 333 patients with depression and 378 age- and gender-matched healthy controls. The results were analyzed to identify clusters of abnormal connectivity that were associated with different combinations of clinical features of depression. The cluster-discovery analysis was developed in a sample of 220 patients and then applied to the full set of patients and controls to determine diagnostic accuracy.

Results: The analysis identified a group of abnormalities that was common to all depressive subtypes and that differentiated them from controls. These abnormalities were located in the insula, orbitofrontal cortex, ventromedial prefrontal cortex, and multiple subcortical sites. Three symptoms quantified by the 17-item Hamilton Rating Scale for Depression were present in nearly all patients with depression: low mood, anhedonia, and anergia/fatigue. Abnormal connectivity in the common areas was associated with severity scores for these 3 symptoms.

In addition, the analysis identified biotypes—i.e., groups that were maximally dissimilar from one another. This analysis resulted in a 4-cluster solution, with some overlap. (See table.) Functions of the affected structures in each cluster were associated with different symptoms of depression. Differences in symptoms did not reflect differences in overall depression severity, which was comparable in biotypes 1, 3, and 4 and modestly but significantly decreased in biotype 2.

Depression biotypes: Affected brain regions and clinical correlates

Biotype	Abnormal Connectivity	Function of Affected Region	Symptoms
1	Frontoamygdala networks (reduced)	Fear-related behavior, reappraisal of negative emotional stimuli	Anxiety
	Anterior cingulate & orbitofrontal areas (reduced)	Motivation, incentive-salience evaluation	Anergia, fatigue
2	Anterior cingulate & orbitofrontal areas (reduced)	Motivation, incentive-salience evaluation	Anergia, fatigue
3	Thalamic & frontostriatal networks (increased)	Reward processing, adaptive motor control action, initiation	Anhedonia, psychomotor retardation
4	Frontoamygdala networks (reduced)	Fear-related behavior, reappraisal of negative emotional stimuli	Anxiety
	Thalamic & frontostriatal networks (increased)	Reward processing, adaptive motor control action, initiation	Anhedonia, psychomotor retardation

Based on the connectivity features of the 4 clusters, overall diagnostic accuracy was as high as 89%. Individual patients and controls were identified with sensitivities* ranging from 84% to 91% and specificities* ranging from 84% to 93%. Biotype diagnosis was stable over time, according to second fMRI scans conducted in 50 patients who were still experiencing depression 4–6 weeks after the first scan; 90% remained in their original biotype.

A total of 124 patients received high-frequency rTMS of the dorsomedial prefrontal cortex for 5 weeks, beginning soon after the first fMRI scan. Treatment response varied significantly according to cluster membership (p=0.00001). rTMS was most effective in biotype 1 patients; 83% improved substantially. Improvement rates were 61% for biotype 3, 30% for biotype 4, and 25% for biotype 2. Classification according to biotype and connectivity features correctly predicted response or nonresponse to rTMS in 90% of patients. In contrast, clinical symptoms were a relatively poor predictor of response.

Discusssion: Although these results require replication, they appear to provide a novel classification system that could overcome some of the shortcomings of the current diagnostics, as well as allow for better identification of individual patients who are most likely to benefit from targeted neurostimulation therapies.

Drysdale A, Grosenick L, Downar J, Dunlop K, et al: Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine* 2016; doi 10.1038/nm.4246. From Weill Cornell Medical College, New York, NY; and other institutions. **Funded by the NIMH; and other sources. The authors declared financial relationships with commercial sources.**

***See Reference Guide.**

Diabetes Risk in Schizophrenia

According to a population-based cohort study, schizophrenia confers a 3-fold increase in risk for early-onset diabetes, which is further increased 3-fold with the use of antipsychotic drugs. First- and second-generation antipsychotics do not differ in the amount of added risk.

Methods: The study cohort included all persons born in Denmark in 1977 or later and included >2.7-million people followed for a mean of nearly 19 years. Incidence of diabetes and information on all dispensed antidiabetic prescriptions was ascertained from Danish national hospital and prescription registries. Because diabetes type was not specified in the databases, the investigators could not distinguish between type 1 and type 2 diabetes. The national psychiatric research registry was used to identify all patients who received a diagnosis of schizophrenia after 1995, when the registry data was deemed complete.

Results: Over the study period, almost 9000 (0.33%) cohort members received a diagnosis of schizophrenia, and diabetes developed in >14,000 (0.52%). Those with schizophrenia were significantly more likely to have a family history of diabetes than cohort members without schizophrenia (p<0.0001).

Among people who were not exposed to antipsychotics, diabetes had onset in 0.5% of those without schizophrenia and 0.9% of those with schizophrenia (hazard ratio,* 3.07 after adjusting for other risk factors including family history and the use of other diabetogenic medications). About half of patients with schizophrenia were antipsychotic-naive at the time of their diagnosis. After antipsychotics were prescribed, patients had a further increase in risk of diabetes (adjusted hazard ratio, 3.64 compared with before antipsychotic use).

Although diabetes risk did not differ between patients started on a first- or second-generation antipsychotic, separate analyses were conducted for selected antipsychotics. Starting aripiprazole or olanzapine was associated with a nearly 2-fold increase in risk in addition to the elevation associated with patients' prior medication. Starting clozapine resulted in another 4-fold increase in diabetes risk, compared with people with schizophrenia not receiving clozapine (hazard ratio, 3.98).

Discussion: Patients with schizophrenia aged <40 years are known to be at high risk of early-onset type 2 diabetes, which is a severe and rapidly progressive diabetes subtype. Few previous studies have focused on the risks of early-onset diabetes in antipsychotic-naive patients with schizophrenia, the additional effects of antipsychotic drugs, and the relative risks

of first- and second-generation antipsychotics. The present study does not support a suggested protective effect of aripiprazole, although it may have been prescribed more often for diabetes-prone patients in this cohort.

Rajkumar A, Horsdal H, Wimberley T, Cohen D, et al: Endogenous and antipsychotic-related risks for diabetes mellitus in young people with schizophrenia: a Danish population-based cohort study. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2016.16040442. From Kings College London, U.K.; and other institutions. **Funded by the European Community's Seventh Framework Programme. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

Common Drug Trade Names*: aripiprazole—*Abilify*; clozapine—*Clozaril*; olanzapine—*Zyprexa

***See Reference Guide.**

Dried Blood Spot Sampling for Home Drug Monitoring

According to a review, dried blood spot sampling may offer the potential for therapeutic drug monitoring (TDM) of some psychiatric drugs using samples obtained by the patient at home.

Dried blood spot samples are obtained by spotting a drop of blood (via finger prick) on to filter paper. Assays to analyze samples obtained by dried blood spot sampling have been in development for at least a decade, but their potential in psychiatry remains largely unexplored. TDM is routinely indicated for tricyclics, lithium, valproic acid, carbamazepine, and clozapine. Routine TDM of antipsychotics is a matter of debate. Possible advantages of using dried blood spot sampling rather than traditional blood sampling include convenience, low cost, noninvasiveness, the small amount of blood required, no risk of contaminating the environment, and the ability to capture trough or 12-hour drug concentrations outside the hospital. Dried blood spot sampling also has the potential for obtaining blood counts and clinical chemistry data used in psychiatry, such as renal and thyroid function.

A literature search identified 15 studies evaluating dried blood spot sampling for psychiatric drugs: 12 assay validation studies, of which 5 were also clinical validation studies, and 3 additional clinical validation studies. No implementation studies were identified. The identified studies included 2 assays for clozapine; 1 for ziprasidone; 3 each for valproic acid, carbamazepine, and lamotrigine; and various assays for tricyclic, SSRI, SNRI, and NRI antidepressants. Although TDM is mandatory for lithium, DBS assays for lithium have not yet been developed. When performed, the clinical validation studies generally showed high correlation with gold-standard assays.

An important disadvantage of DBS is the risk of poor sampling due to its reliance on the patient. Another is that results are affected by the amount of blood spotted on the filter paper—the so-called hematocrit effect. Methods to correct for this effect are being investigated.

Martial L, Aarnoutse R, Mulder M, Schellekens A, et al: Dried blood spot sampling in psychiatry: perspectives for improving therapeutic drug monitoring. *European Neuropsychopharmacology* 2017; doi 10.1016/j.euroneuro.2017.01.009. From Radboud University, the Netherlands. **This review was conducted without funding. The authors declared no competing interests.**

Common Drug Trade Names*: carbamazepine—*Tegretol;* clozapine—*Clozaril*; lamotrigine—*Lamictal*; valproic acid—*Depakene, Depakote*; ziprasidone—*Geodon

Cognitive Control Training in Depression

In a randomized trial, cognitive control training (CCT), a computer-based intervention designed to strengthen the dorsolateral prefrontal cortex (DLPFC), did not enhance the antidepressant effects of brief behavioral activation therapy.

Background: CCT is designed to activate and strengthen the DLPFC and correct the hypoactivity in this region during depressive episodes. It has not previously been tested in combination with a psychosocial treatment, but it has been shown to be effective in intensive outpatient settings and when used in combination with transcranial direct current stimulation.

Methods: In the study, CCT consisted of 2 computerized training tasks that focused on attention and inhibition and took about 25 minutes to complete. CCT was compared with an inactive control computerized task. Participants were 34 adults (mean age, 36 years) with a primary diagnosis of major depressive disorder, either unmedicated or on long-term stable antidepressant medication. All participants received an abbreviated form of behavior activation therapy, which was condensed from 10 to 4 sessions. Patients participated in CCT or the comparison task in the laboratory preceding each of the 4 behavioral activation sessions. The primary efficacy outcome was change in the Beck Depression Inventory-II (BDI-II) from baseline to 5 weeks (1 week after the last treatment). Response was defined as a decrease of ≥47% in the BDI-II and remission as a final score of ≤12.

Results: Patients in both treatment groups showed significant decreases in BDI scores (p=0.05), as well as secondary outcome measures including the Montgomery-Asberg Depression Rating Scale (p=0.01) and the Ruminative Responses Scale (p=0.05). However, there were no statistically significant differences between CCT and the control task for any of these outcomes, nor did the results differ in an analysis limited to treatment completers, in which response rates were 31% for CCT and 42% for the control condition. All responders also achieved remission.

Discussion: Although adjunctive CCT did not provide additional benefits in this study sample, the large improvements with abbreviated behavioral activation therapy are encouraging. Possible reasons for the lack of effect in this study include less frequent administration than in other studies and overshadowing by the robust effects of behavioral activation. It is also possible that effects of CCT may be limited to patients with demonstrated DLPFC hypoactivity.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial, but the source of funding was not stated.

Moshier S, Otto M: Behavioral activation treatment for major depression: a randomized trial of the efficacy of augmentation with cognitive control training. *Journal of Affective Disorders* 2017; doi 10.1016/j.jad.2017.01.003. From Boston University, MA. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

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Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Sensitivity and Specificity: Statistical measures of the performance of binary classification tests. Sensitivity measures the proportion of actual positives that are correctly identified (i.e., the percentage of sick people who are correctly identified as having the condition). Specificity measures the proportion of negatives that are correctly identified (i.e., the percentage of healthy people who are correctly identified as not having the condition). A perfect predictor would have 100% sensitivity and specificity.

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. The checklists are posted at www.alertpubs.com.

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Self-Guided Internet CBT for Depressive Symptoms

According to a meta-analysis of individual participant data from randomized trials, self-guided internet-based cognitive behavioral therapy (iCBT) has modest but significant antidepressant effects. This suggests that iCBT may be a viable first-step treatment, particularly for those wishing to avoid therapist contact.

Background: Previous conventional meta-analyses of iCBT have had inconsistent results. The present study evaluated individual patient data as a means of maximizing the study's power to detect a true effect.

Methods: The analysis included randomized trials of adults with elevated levels of depressive symptoms based on any diagnosis or self-reported symptom scale. Control conditions were usual care, a waiting list, or an attention control. Authors of eligible articles were contacted and asked to provide individual-level data. Treatment response was defined as a ≥50% improvement from baseline in depressive symptoms. The study design allowed analysis of a variety of individual-level variables such as sociodemographic data, baseline symptom severity, and treatment adherence.

Results: Of 16 studies that met selection criteria, individual-level data were available from 13, with a total of nearly 3900 participants. Treatment ranged from 5 to 11 online sessions. Four programs provided technical support, while 7 were entirely self-guided. About 2% of patients did not begin treatment after enrolling in a study, and 27% dropped out without providing post-treatment data. The studies were judged to have low risk of bias.

At follow-up, which ranged from 6 to 16 weeks after randomization, self-guided iCBT had a significantly greater positive effect than the control treatments on depressive symptoms (effect size,* 0.27; $p<0.001$). Of multiple participant-level factors analyzed, only treatment adherence was significantly predictive of a better outcome ($p=0.001$). iCBT had a positive effect on treatment response ($p<0.001$), with an odds ratio* of 1.95 vs. placebo and a number

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needed to treat* of 8. None of the sociodemographic or clinical variables predicted response, other than adherence ($p<0.001$).

Discussion: The lack of association between outcome and patient-level variables suggests iCBT can be used by most individuals with depressive symptoms, regardless of symptom severity or sociodemographic background. Despite its limitations, including high dropout rates and potentially small effects compared with face-to-face interventions, these results suggest iCBT could provide treatment at a low cost to large numbers of patients.

Study Rating*—18 (100%): This study met all criteria for a meta-analysis.

Karyotaki E, Riper H, Twisk J, Hoogendoorn A, et al: Efficacy of self-guided internet-based cognitive behavioral therapy in the treatment of depressive symptoms: a meta-analysis of individual participant data. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.0044. From Vrije Universiteit Amsterdam, the Netherlands; and other institutions. **Funded by the European Commission's Seventh Framework Program. One study author disclosed financial relationships with commercial sources; the remaining 25 authors declared no competing interests.**

***See Reference Guide.**

Emotion Regulation Therapy for Distress Disorders

Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are sometimes referred to as "distress disorders" because they are often associated with profound suffering and tend to be refractory. They are frequently comorbid and may share neurobehavioral characteristics. Emotion regulation therapy (ERT) is a relatively new, manualized intervention for distress disorders that may address underlying mechanisms and that is supported by preliminary evidence.

The term distress disorders was derived primarily from studies showing high diagnostic comorbidity and a surface resemblance between GAD and MDD. Further investigation has identified shared etiological factors: intense emotional experiences resulting in caution and negative self-referential processing (NSRP), such as worry, rumination, and self-criticism. Persons with distress disorders lack the ability to resolve emotion-driven motivational conflicts between systems that balance reward versus loss and safety versus threat. Rather than processing emotional information for its motivational value, they may fail to regulate their emotions in a context-appropriate manner. The high prevalence of NSRP behaviors may explain the refractoriness of distress disorders. Patients are also prone to narrow and rigid contextual learning, with inflexible repertoires of response to negative situations.

ERT is a manualized intervention consisting of 16 weekly sessions that target motivational mechanisms, regulatory mechanisms (both NSRPs and behaviors such as avoidance), and contextual learning. The first phase of ERT consists of learning mindful emotion regulation skills to promote intentional and flexible responses to intense experiences of emotions such as anxiety, anger, and sadness. These skills are taught by practice, followed by meta-cognitive regulation. In the second phase, ERT focuses on behavioral proactivity: helping clients identify what is meaningful in their lives, how anxiety and depression stand in the way, and how to take action to reflect their personal desires and values.

To date, ERT has been administered in university-based treatment centers, by doctoral students in clinical psychology who were trained by the developers of the intervention. An earlier, 20-session version of ERT was evaluated in a preliminary trial in 20 adults with GAD, with or without depression. Treatment was well tolerated and was associated with reduced clinician-assessed and self-reported symptoms of GAD severity, worry, trait anxiety, and depression symptoms, as well as improvement in quality of life, with effect sizes* ranging from 1.5 to 4.5. A randomized trial conducted in 63 adults showed comparable improvement with ERT and a wait-listed control, with a similar range of effect sizes (0.50–2.0). In both studies, beneficial

effects of ERT persisted for 9 months. In a subset of patients with comorbid GAD and MDD, ERT also reduced depression-related outcomes such as rumination and anhedonia. The current 16-session version of ERT was also tested in an open-label trial in a culturally and socioeconomically diverse sample of 32 young adults with a primary diagnosis of any anxiety or mood disorder. Again effect sizes were generally large for a variety of positive outcomes, and gains were maintained during follow-up. Additional research in the laboratory has shown that the treatment outcomes are related to changes in the hypothesized underlying mechanisms of distress disorder, such as attentional flexibility.

While the limited amount of clinical research has shown positive results with ERT, the findings are preliminary. Ongoing studies continue to evaluate transdiagnostic efficacy as well as the effects of patient demographics. Additionally, the minimum effective "dose" of ERT has yet to be established and trials of a shortened 8-session intervention are underway.

Renna M, Quintero J, Fresco D, Mennin D: Emotion regulation therapy: a mechanism-targeted treatment for disorders of distress. *Frontiers in Psychology* 2017; doi 10.3389/psyg.2017.00098. From City University of New York, NY; and other institutions. **Source of funding not stated. The authors declared no financial relationships with commercial sources; however, they are the developers of the ERT protocol.**

***See Reference Guide.**

Brain Stimulation for Refractory Anorexia Nervosa

Deep brain stimulation (DBS) of the subcallosal cingulate was feasible and well tolerated in a group of patients with highly refractory anorexia nervosa. Treatment improved mood and anxiety and was followed several months later by weight gain.[1]

Background: A previous pilot study found DBS had positive effects on mood symptoms and body weight after 9 months of follow-up in 3 of 6 patients with life-threatening, refractory anorexia nervosa.[2] The present study, conducted by the same researchers, extends those findings over a longer term in a larger group of patients.

Methods: Study participants were adults, aged 20–60 years, with anorexia nervosa that was highly chronic or resistant, as defined by unresponsiveness to multiple voluntary hospitalizations, increasing medical instability, poor response to or refusal to participate in intensive expert treatment, and a 10-year pattern of chronic stable anorexia with increasing medical acuity, including involuntary feedings in the past 2 years. All patients underwent surgical placement of electrodes under local anesthesia for active stimulation mapping. With the patient under general anesthesia, electrodes were then internalized and a subcutaneous pulse generator was implanted. The stimulator was activated during a follow-up visit 10–14 days after discharge. Stimulation was increased after 1 month as tolerated. Medication was kept stable for the first 3 months. Patients were evaluated at 1, 3, 6, and 12 months post-activation. The primary outcome was safety and acceptability of the procedure. Secondary outcomes included body mass index (BMI), anorexia-specific behaviors, mood, anxiety, and changes in neural circuitry (measured with PET imaging).

Results: A total of 16 patients, including the 6 from the initial trial, underwent DBS. All were women with a mean duration of illness of 18 years and a mean age at electrode implantation of 34 years. All had a significant history of medical nonresponse, including multiple hospitalizations.

There were few serious adverse events related to surgery: 5 patients had incision-related pain lasting more than a few days, and 1 patient had a surgical site infection that did not respond to antibiotics, resulting in removal of the device. The latter patient requested and received another device 6 months later. Two patients requested device deactivation—1 following weight

restoration, possibly because of discomfort with the weight gain, and another for unknown reasons. One patient had a seizure several months after the surgery, for reasons that could not be identified. There were no deaths, intracranial hemorrhages, or stimulation-related side effects.

Mean BMI increased from 13.8 at baseline to 17.3 at 12 months (p=0.0009; effect size,* 1.34). Of the 14 patients with 12 months of follow-up, 6 achieved a normal BMI of ≥18.5. Changes in weight did not begin to appear until ≥3 months after treatment.

Of 8 patients with significant binge eating, 3 experienced remission and another had a 91% improvement. Of 11 patients with purging behaviors, 4 became completely abstinent and another 4 had reductions of ≥50%. Scores on the Yale-Brown Obsessive Compulsive Scale improved significantly during the year (p=0.023), as did measures of eating-disorder-specific psychopathology (preoccupations and rituals; p≤0.02). Measures of depression and anxiety also showed significant improvement (p≤0.035 for all; effect size, 0.55–1.5). A ≥50% decrease in Hamilton Rating Scale for Depression score was achieved by 10 of 14 patients (71%) and a ≥50% decrease in Beck Anxiety Inventory score was achieved by 4 of 16 patients (25%). Quality-of-life scores were also significantly improved at 12 months (p=0.02). PET scans at baseline and 12 months indicated alterations in cerebral glucose metabolism comparable with the hypothesized mechanisms of anorexia nervosa.

Discussion: The safety and feasibility of DBS in this study is consistent with experience reported in other disorders. The finding that weight gain lagged behind early improvement in mood and anxiety suggests that improvement in limbic dysfunction might precede or enable later changes in weight. These results highlight the importance of treating illness-maintaining factors rather than focusing only on weight.

[1]Lipsman N, Lam E, Volpini M, Sutandar K, et al: Deep brain stimulation of the subcallosal cingulate for treatment-refractory anorexia nervosa: 1 year follow-up of an open-label trial. *Lancet* 2017; doi 10.1016/s2215–0366(17)30076–7. From the University of Toronto, Canada; and other institutions. **Funded by the Klarman Family Foundation; and the Canadian Institutes of Health Research. Two study authors disclosed financial relationships with commercial sources; the remaining 8 authors declared no competing interests.**

[2]Lipsman N, et al: Subcallosal cingulate deep brain stimulation for treatment refractory anorexia nervosa: a phase 1 pilot trial. *Lancet* 2013;381 (April 20):1361–1370. See *Psychiatry Alerts NOS* 2013;5 (June):31–32.

***See Reference Guide.**

Vestibular Stimulation and Insight in Schizophrenia

Impaired insight into illness is common in schizophrenia and may be the most treatment-resistant manifestation. Vestibular stimulation produced transient insight improvement in a small controlled trial in patients with schizophrenia.

Background: Imaging studies have suggested impaired insight is associated with reduced right hemispheric grey-matter volume and left hemisphere dominance. Caloric vestibular stimulation (CVS), via the infusion of cold or warm water into the external ear canal, stimulates the vestibular nerve by inducing a temperature gradient across the semicircular canals. According to case reports, CVS can transiently improve impaired insight into illness.

Methods: The present study was conducted to assess the effects of CVS in patients in a controlled manner, using a validated measure. Participants were 16 adults with schizophrenia or schizoaffective disorder with moderate-to-severe impairment of insight, defined as a score of ≥3 on the "Lack of judgment and insight" item on the Positive and Negative Syndrome Scale. Patients were not informed of the rationale for the intervention or the expected outcome. All patients received 3 treatments, in randomized order: CVS with iced water (39 degrees) into the right ear, CVS with iced water into the left ear, and body-temperature water (the sham condition) into a randomly-chosen ear. Irrigation lasted 30 seconds or until the patient could not tolerate

the resulting vertigo, nausea, or discomfort. Eye movements were calibrated during a cognitive task to measure the peak slow phase velocity (PSPV) of nystagmus, a measure of vestibular reactivity. The primary measure of illness-related insight was the 10-item VAGUS-self-report version, which is sensitive to small changes and reflects 4 core dimensions of illness-related insight. The VAGUS-SR was administered before and 30 minutes after each CVS treatment.

Results: CVS was well tolerated, with only transient symptoms of vertigo and minor nausea. Results of the experiment varied according to patients' PSPV reactivity to body-temperature CVS. In participants with greater vestibular reactivity (i.e., higher PSPV), both cold and body temperature CVS to the left ear improved illness-related insight in comparison to right cold CVS, which decreased insight ($p=0.001$ for left cold vs right cold; $p=0.042$ for right cold vs body temperature). Of the 4 subscales of the VAGUS-SR, post-treatment change in the General Illness Awareness dimension following left cold CVS was positively associated with vestibular reactivity. Left and right cold CVS were associated with improvement and worsening, respectively, in mood and positive symptom severity, although these changes were not statistically significant. Persistence of the improvements in insight beyond 30 minutes was not evaluated.

Discussion: Although there is no conclusive link between psychopathology and vestibular dysfunction in schizophrenia, underactive circuits in the right hemisphere (e.g., posterior parietal and medial prefrontal cortex) have been implicated in insight deficits in schizophrenia spectrum disorders. It is possible that left cold CVS improves insight by stimulating these underactive circuits. If the positive results can be replicated in more stringent studies, this safe, easy-to-administer, non-invasive intervention could substantially improve outcomes in schizophrenia by increasing patients' illness recognition and treatment engagement. Other methods of vestibular stimulation should be considered in future studies as well.

Gerretsen P, Pothier D, Falls C, Armstrong M, et al: Vestibular stimulation improves insight into illness in schizophrenia spectrum disorders. *Psychiatry Research* 2017;251:333–341. From the Centre for Addiction & Mental Health, Toronto, Canada; and other institutions. **Funded by the Ontario Mental Health Foundation; and other sources. Two study authors declared financial relationships with commercial sources; the remaining 7 authors declared no competing interests.**

Probiotics and Depressive Symptoms

According to a review of limited evidence, daily consumption of a probiotic supplement could improve mood, anxiety, and cognitive symptoms in patients with depression.

Background: Recent neurogastroenterology research has identified direct biochemical signaling between the gastrointestinal (GI) tract and the CNS. Called the gut–brain axis, this communication network is bidirectional and engages the autonomic nervous system, enteric nervous system, neuroendocrine system, and immune system. CNS disorders such as depression have been linked to changes in the GI microbiome, leading to the suggestion that manipulating the microbiome can relieve depressive symptoms. Research has employed either a whole-diet approach or individual supplements—mainly probiotics, which are live microorganisms that transiently colonize the GI tract and influence various signaling pathways.

Methods: A comprehensive literature review identified 10 peer-reviewed, medium-to-high-quality trials that assessed the effects of probiotics on mood, anxiety, and/or cognition in human subjects. Of these, 7 were conducted in healthy individuals and 1 each in patients with depression, stress or exhaustion, and chronic fatigue syndrome. The most frequently studied probiotic strain was *Lactobacillus casei*. Treatment durations ranged from 3 weeks to 6 months.

Results: Of 5 studies that examined the effects of probiotics on mood symptoms, 3 reported positive results. Notably, an 8-week placebo-controlled trial in 40 patients with depression reported a significant treatment-related decrease in Beck Depression Inventory scores. Two

other studies, in healthy subjects, showed that a probiotic supplement reduced somatization, depression, and anger-hostility scores on the Hopkins Symptom Checklist (HSCL-90); the supplement also reduced cognitive reactivity to depression, in particular aggressive and ruminative thoughts. A study of probiotics in healthy older adults and another in patients with chronic fatigue syndrome found no effect on mood.

Of 7 studies that examined the effect of probiotics on stress and anxiety, 5 found a positive effect. In 1 study of 42 persons suffering from stress and exhaustion, 6 months of probiotic consumption was associated with overall improvement, and three-fourths of patients rated the treatment as good or very good. Three studies tested the effect of probiotics on various aspects of cognition, all reporting positive effects on such indicators as neuropsychological test performance, problem-solving, self-blame, and cognitive fatigue.

Discussion: Results of studies in rodents suggest consumption of probiotics prevents increases in biomarkers of chronic stress and increases production of brain-derived neurotrophic factor, which is abnormally low in patients with depression. Consumption of probiotics has also been shown to influence the biosynthesis and metabolism of serotonin, reduce pro-inflammatory cytokines, and induce positive changes in behavioral indicators of anxiety and depression.

Probiotic supplementation may exert anxiolytic and antidepressant effects via regulation of inflammatory markers and serotonin neurotransmission. While there are considerable gaps in the existing research—including a lack of studies in patients with well-defined depression and uncertainty about the most effective bacterial strains and the optimal dosing and duration of treatment—further study appears to be warranted.

Wallace C, Milev R: The effects of probiotics on depressive symptoms in humans: a systematic review. *Annals of General Psychiatry* 2017; doi 10.1186/s12991–017–0138–2. From Queen's University, Canada. **Source of funding not stated. The authors disclosed financial relationships with commercial sources.**

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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.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

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. The checklists are posted at www.alertpubs.com.

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Follow-Up After Suicide Attempt

According to the results of an observational study, telephone follow-up after a suicide attempt may protect against repeated suicidal gestures.

Methods: Study participants were adults who received treatment for a suicide attempt at a single institution in France in 2010. The intervention started with a pre-discharge meeting with a nurse, who evaluated patients' suicide potential using a standard scale and then informed the patient that they would receive 3 follow-up calls over the next 2 months. Following discharge, patients received the telephone calls after about 8, 30, and 60 days. If calls were not answered or messages not returned within 24 hours, patients were immediately contacted by text, email, or letter, with additional follow-up letters within 7 days and monthly thereafter for 5 months. The calls assessed suicide risk and medication compliance. A comparison group consisted of all suicidal patients seen at the unit in the prior year who received usual treatment but no telephone follow-up. The primary study outcome was a repeated suicidal act.

Results: A total of 436 patients received telephone follow-ups, and 387 were included in the no-intervention comparison group. The majority of patients (56%) answered all 3 follow-up calls, and 12% did not respond to any.

A total of 55 patients in the intervention group and 69 controls had a repeat suicide attempt during follow-up (13% vs 18%; p=0.037; odds ratio,* 0.67). Risk of repeat attempt was lowest in patients who responded to all 3 telephone calls (odds ratio, 0.50). When odds ratios were calculated for time period following each of the phone calls, the difference from controls was significant only following the second call, between 30 and 60 days post-discharge (odds ratio, 0.31). Results remained essentially unchanged in a multivariate analysis that included patients' history of psychiatric disorders and treatment.

Exbrayat S, Coudrot C, Gourdon X, Gay A, et al: Effect of telephone follow-up on repeated suicide attempt in patients discharged from an emergency psychiatry department: a controlled study. *BMC Psychiatry* 2017; doi 10.1186/s12888-017-1258-6. From the University Hospital, Saint-Etienne, France; and other institutions. **Funded by the Regional Public Health Group of the Rhone-Alpes. The authors declared no competing interests.**

***See Reference Guide.**

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New DBS Target

Deep brain stimulation of the supero-lateral branch of the medial forebrain bundle (slMFB) showed preliminary efficacy in a small, long-term, uncontrolled study in patients with highly refractory depression.

Methods: Study participants were 8 patients who received DBS of the slMFB for up to 48 months. All patients had severe treatment-resistant depression, including 1 with bipolar disorder whose last manic episode was 23 years earlier. Drug treatment was kept unchanged for ≥6 weeks before and after implantation of the DBS device. The primary outcome measure was change from baseline to 12 months on the Montgomery-Asberg Depression Rating Scale (MADRS), using the following cutoffs: partial response, 25% reduction; clear response, 50% reduction; strong response, 75% reduction; remission, score <10. An alternative, timeline method of analysis evaluated MADRS scores during each of 3 baseline months and then every 3 months post-treatment for 4 years.

Results: Patients ranged in age from 30 to 55 years and had severe treatment-resistant depression, refractory to multiple drugs, psychotherapy, and ECT. Patients' current episode had a mean duration of 7 years; each had received treatment with a mean of 19 antidepressants, with an average of 4 in use at the time of implantation.

After 1 year of DBS, 6 patients were classified as clear responders, including 3 who were strong responders and 4 who achieved remission. One additional patient achieved a 50% response for several months of the first year, and 1 patient never achieved response.

Mean MADRS scores were significantly reduced from baseline during each month of treatment. The mean score decreased from about 30 at baseline to 10.5 at 12 months ($p<0.005$). DBS also produced significant improvement on secondary measures of depression (Hamilton Rating Scale for Depression and Beck Depression Inventory; $p=0.001$ and $p<0.05$, respectively), and anxiety (Hamilton Anxiety Rating Scale; $p<0.05$). Average scores on the Global Assessment of Function decreased from 41 (serious impairment) to 73 (no more than slight impairment; $p=0.001$).

Oculomotor side effects of DBS were common but easily corrected. The patient who had no response stopped treatment after month 18, followed by a worsening of depression. Another patient, despite experiencing a remission, requested explantation of the device at month 27, against medical advice. He retained his remission for ≥1 year. The course of depression fluctuated considerably in several patients, owing to life events and medication noncompliance.

Discussion: This study showed a large statistical effect in a small, highly selected sample. The rapid and sustained antidepressant effects (evident after 1 month and through 48 months) suggest the slMFB is an effective target, and additional research appears to be warranted. Other DBS targets have shown promise in preliminary studies, only to fail in larger controlled clinical trials.

Bewernick B, Kayser S, Gippert S, Switala C, et al: Deep brain stimulation to the medial forebrain bundle for depression—long-term outcomes and a novel data analysis strategy. *Brain Stimulation* 2017; doi 10.1016/j.brs.2017.01.581. From the University of Bonn, Germany; and other institutions. **Funded by Medtronic; and other sources. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

Bright Light Therapy in ADHD

In a pilot study, bright light therapy improved delayed sleep timing as well as symptoms of hyperactivity and impulsivity in adults with ADHD.

Background: Sleep disturbances often accompany ADHD, may be worsened by long-acting stimulants, and may in turn contribute to deficits in executive function and attention. These

disturbances may be associated with deficits in the underlying circadian clock, and manipulating the nocturnal rise in melatonin, measured as dim-light melatonin onset (DLMO), with bright light therapy has been suggested as a potential complementary therapy in patients with ADHD.

Methods: Study participants were 7 men and 9 women (mean age, 36 years) who met DSM-IV criteria for ADHD, and were not taking medication for any non-ADHD psychiatric disorder. Those taking ADHD medications were allowed to continue on stable doses but were required to take all of their medication before noon; those taking stimulants were strongly urged to take their medication by 8 AM. Participants were provided a light box (10,000 lux) for 30 minutes of morning bright light therapy daily for 2 weeks in their home. In addition, participants wore a wrist actigraph continuously and kept diaries of sleep and light box usage. They were instructed to use the light box 3 hours after their calculated mid-sleep time, the midpoint between sleep onset and waking, as determined by actigraphy. They were also advised to avoid overhead light and wear blue light-blocking sunglasses outdoors after 4 PM to avoid suppressing melatonin onset. Participants spent a night in the temperature- and light-controlled research unit at baseline and again after completing bright light therapy, in order to provide hourly saliva samples for assessment of DLMO and measure ADHD symptoms and other outcomes. The primary outcome measures were timing of DLMO, a well validated endogenous clock phase marker, and mid-sleep time. Secondary measures included the ADHD Rating Scale (ADHD-RS) and measures of sleep quality.

Results: Bright light therapy advanced the timing of DLMO by a mean of 31 minutes, from 8:36 to 8:05 PM (p=0.002) and advanced mid-sleep time by 57 minutes, from 4:37 AM to 3:40 AM (p=0.004). These changes resulted in a more narrow phase angle (time between DLMO and mid-sleep), changing from 8:11 to 7:44 hours (p=0.001). Advances in DLMO and mid-sleep time were correlated with decreases in the ADHD-RS total score and with the hyperactive-impulsive subscore. Changes in ADHD symptoms were not correlated with phase angle shortening. After bright light therapy, study participants tended to have earlier sleep start and wake up times and greater sleep fragmentation. Subjectively, participants reported reduced sleepiness and improved sleep quality.

Discussion: ADHD symptoms are correlated with circadian disruption at multiple levels. Adults with ADHD report excess daytime sleepiness and later bed/wake-up times, and they have documented disruptions in sleep-activity cycles. Results of this pilot study suggest that bright light therapy can improve these alterations, which may lead to improvement in ADHD symptoms. Randomized, controlled trials appear to be warranted.

Fargason R, Fobian A, Hablitz L, Paul J, et al: Correcting delayed circadian phase with bright light therapy predicts improvement in ADHD symptoms: a pilot study. *Journal of Psychiatric Research* 2017; doi 10.1016/j.psychires.2017.03.004. From the University of Alabama at Birmingham. **Funded by the university. The authors declared no competing interests.**

Vagus Nerve Stimulation for Resistant Depression

According to the results of a post-marketing surveillance study required by the FDA, adding vagus nerve stimulation (VNS) to treatment as usual produced better long-term outcomes in patients with treatment-resistant depression.

Methods: The Treatment-Resistant Depression Registry, maintained by Cyberonics Inc. as a condition of FDA approval for their VNS device, enrolled patients from 61 U.S. sites. Participants had a current unipolar or bipolar major depressive episode of ≥2 years in duration, or ≥3 prior episodes, and a history of nonresponse to 4 prior treatments, including maintenance pharmacotherapy, psychotherapy, and ECT. Patients were allowed to select VNS or treatment as

usual, although some were denied VNS for financial/other reasons. Participants in the VNS arm, which included those in the manufacturer's dose-finding study, underwent device implantation before the baseline visit. Patients were followed every 3 months for a year, and then at 6-month intervals for the next 4 years. Patients also received follow-up telephone calls from nurses trained to assess suicidality. The primary efficacy outcome measure was the Montgomery-Asberg Depression Rating Scale (MADRS). Outcomes were adjusted using propensity scores* for baseline prognostic factors. Suicidality and mortality were the primary safety endpoints of the study.

Results: The registry included 494 patients who received VNS (including 159 from the dose-finding study) and 301 who received treatment as usual. Of patients who received VNS, about 58% had recurrent major depression, 14% had single-episode major depression, and 28% had bipolar I or II disorder. The mean number of failed prior treatments was 8 in the VNS arm and 7 in the control arm. Patients in the VNS arm had more severe depression than the treatment-as-usual arm, as suggested by higher baseline depression rating scores and more prior psychiatric hospitalizations and suicide attempts.

About two-thirds of patients in the VNS arm and nearly half of controls completed 5 years of follow-up. Response and remission rates were significantly higher with VNS than treatment as usual. (See table.) Throughout the study, the cumulative percentage of first-time responders in the VNS arm was about double that of the control arm. Secondary efficacy measures—the Clinical Global Impression–Improvement scale and the Quick Inventory for Depressive Symptomatology–Self Report (QIDS-SR)—showed a similar pattern to the MADRS results. Patients who received VNS had a shorter time to first response and a longer duration of response than controls. Response and remission rates with both treatments were higher in patients previously responsive to ECT than in ECT nonresponders, and differences between VNS and control treatment were preserved in these subgroup analyses.

Five-year efficacy results: vagus nerve stimulation vs treatment as usual

Endpoint	VNS	Treatment as Usual	Significance
Cumulative response rate[†]	67.6%	40.9%	p<0.001
Remission rate[††]	43.3%	25.7%	p<0.001
Time to first response	12 months	48 months	p<0.001
Response duration	12 months	7 months	p=0.001

[†]Response: ≥50% improvement in MADRS score
[††]Remission: MADRS score ≤9 at any postbaseline visit

Both treatment arms showed improvement in suicidality, with the VNS arm showing a significantly larger reduction in the suicidality item on the QIDS-SR and in an investigator-completed suicidality assessment. All-cause mortality was significantly lower in the VNS arm (3.53 vs 8.63 per 1000 person-years). There were 2 completed suicides in each group, half the rate with VNS as with treatment as usual.

Aaronson S, Sears P, Ruvuna F, Bunker M, et al: A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: comparison of response, remission, and suicidality. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.16010034. From the Sheppard Pratt Health System, Baltimore, MD; Cyberonics Inc., Houston, TX; and other institutions. **Funded by Cyberonics Inc. Eight study authors disclosed financial relationships with commercial sources including Cyberonics; the remaining author declared no competing interests.**

***See Reference Guide.**

Reminder Devices and Medication Adherence

Although many patients cite forgetfulness as the main explanation for medication noncompliance, in a randomized trial, simple, inexpensive reminder devices did not improve medication adherence in poorly compliant patients with chronic illnesses.

Methods: Study subjects, aged 18–64 years, were >53,000 enrollees in a large pharmacy-benefits program. Patients had a prescription for 1–3 maintenance medications for a chronic medical or psychiatric illness and had suboptimal adherence, defined as a medication possession ratio (MPR) of 30–80% during the prior 12 months. MPR is the proportion of days for which a patient has obtained the prescribed medication; a perfect MPR is 100%. Patients were randomly assigned to receive 1 of 3 reminder devices—a pill bottle with toggles that can be slid after each day's dose is removed, a pill bottle cap with a digital timer displaying the time elapsed since the most recent dose, and a pill box with 1 compartment for each day of the week—or to a control group that received no reminder device. The primary outcome was the MPR during the 12 months following receipt of the devices, with optimal adherence defined as an MPR ≥80%.

Results: Baseline MPRs ranged from about 40% to 44%. During follow-up, optimal adherence was achieved by 15–16% of patients, with no significant differences between the groups including the no-intervention control. In the cohort of patients taking only antidepressants (n=15,555), the odds ratios* for optimal adherence ranged from 0.93 to 1.02 for the devices, compared with control. Subgroup analyses based on age, gender, baseline level of adherence, and number of targeted medications had similar findings.

Discussion: In surveys of patients with poor medication adherence, up to 60% cited forgetfulness as the main reason. Data on the usefulness of relatively costly electronic-alert devices are limited and inconsistent. The present study results suggest that inexpensive reminder devices may do no better. The larger-than-expected improvement in the control group suggests that nonadherence is a fluctuating target, regardless of intervention. Reminder devices may work better in multicomponent interventions designed to promote both their use and the filling of prescriptions.

Choudhry N, Krumme A, Ercole P, Girdish C, et al: Effect of reminder devices on medication adherence: the REMIND randomized clinical trial. *JAMA Internal Medicine* 2017; doi 10.1001/jamainternmed.2016.9627. From Brigham and Women's Hospital, Boston, MA; and CVS Health, Woonsocket, RI. **Funded by CVS Health. Five study authors disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

***See Reference Guide.**

Treatment Decision Aids in Depression

In a randomized trial, a web-based decision aid increased patients' knowledge and decreased their uncertainty about depression-treatment options.

Background: Previous research indicates that patients with depressive disorders are interested in receiving information about their illness and participating in shared decision making. There have been few studies on the effectiveness of decision support interventions in depression.

Methods: The trial was conducted at 13 primary care practices in Spain. The depression decision aid was developed as part of a web platform to inform patients with highly prevalent chronic medical conditions and engage them in decision-making. Eligible patients with a diagnosis of depression were invited to visit the research center, where they were randomly assigned to use the web-based decision aid or to receive treatment as usual. Patients in the intervention group reviewed the decision aid and completed pre- and post-assessments on the same visit. The decision aid consisted of narratives of real patients' experience, treatment

information including a values clarification exercise, and a section on research needs from the patient's perspective. (At this time, the decision aid is available only in Spanish at www.pydesalud.com.) Participants and controls were evaluated with the Decisional Conflict Scale, a 16-item, 100-point scale evaluating feeling informed, clear values about benefits and risks, support, uncertainty, and effective decision. Treatment knowledge, intention, decisional control preferences, goals, and concerns were evaluated as secondary outcomes.

Results: A total of 68 patients used the decision aid, and 79 acted as controls. Patients had a mean age of 51 years and Beck Depression Inventory scores reflecting moderate depression, with an average duration of 13 years. The majority of patients (85%) were already receiving antidepressant medication, and 3 were receiving psychotherapy.

The decision aid significantly reduced the total score on the Decisional Conflict Scale ($p<0.001$), as well as scores on the informed and effectiveness subscales. Knowledge of treatment options increased significantly ($p<0.001$). Majorities of patients in both groups preferred combined treatment rather than medication or psychotherapy alone.

Most patients who used the decision aid (89–92%) found it useful, easy to navigate, visually appealing, and entertaining; 80% said they would use it for choosing treatment. Three-fourths said that they had learned new things about depression and would ask their physician about these topics. However, 85% thought the decision aid contained too much information.

Discussion: Theoretically, patients would benefit from matching their preferred and received treatment. Use of the decision aid in this study increased concordance between patients' goals and concerns about treatment and their treatment intentions. However, more research is needed to evaluate the effects of this concordance on clinical outcomes.

Perestelo-Perez L, Rivero-Santana A, Sanchez-Afonso J, Perez-Ramos J, et al: Effectiveness of a decision aid for patients with depression: a randomized controlled trial. *Health Expectations* 2017; doi 10.1111/hex.12553. From the Canary Islands Health Service, Tenerife, Spain; and other institutions. **Funded by the Canary Islands Agency for Research, Innovation, and Society of Information. The authors declared no competing interests.**

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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.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias, making it possible to obtain average treatment effects.

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Brief Treatment for Nonsuicidal Self-Injury

In a pilot randomized trial, Treatment for Self-Injurious Behaviors (T-SIB), a brief manualized therapy, was feasible and acceptable in young adults with nonsuicidal self-injury (NSSI), showing modest superiority over treatment as usual.

Methods: Participants (n=33) in the randomized trial were treatment-seeking young adults, aged 18–29 years, who had engaged in NSSI within the past month or who had a history of NSSI and current urges. Patients with active severe suicidal ideation were excluded. T-SIB was designed specifically to treat NSSI behaviors in young adults with or without borderline personality disorder. It consists of 9 weekly, 1-hour, individual sessions that can be delivered as stand-alone or adjunctive treatment. In the early sessions, patients are taught to perform a functional assessment to identify the antecedents and consequences of NSSI. They begin implementing alternative behaviors in the sixth session. Sessions 7 and 8 consist of 1 selection from the 3 available individualized modules: interpersonal communication, cognitive distortions, and distress tolerance. The control treatment consisted of community options for treating NSSI (i.e., encouragement to seek treatment, help finding a therapist, and assistance with scheduling a first appointment) and was offered on multiple occasions throughout the study.

Results: A total of 90 persons responded to advertising for the treatment, 72 completed a telephone screen, 14 were no longer interested or unable to travel for treatment, and 16 did not meet inclusion criteria. Of the remaining 42, 33 attended the baseline assessment, met study criteria, and were randomized. Of these, 79% had engaged in NSSI in the most recent month, with a mean frequency of 10 days/month and an average of 309 acts of NSSI.

A total of 11 patients who received T-SIB and 15 control patients completed a 3-month follow-up assessment. Overall, patients assigned to T-SIB reported high satisfaction with treatment. About half of the treatment-as-usual group received outside treatment during the study, and NSSI was addressed specifically in half of these patients. About 50% of the patients who received T-SIB also sought additional treatment.

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Although the study was underpowered to detect significant differences between T-SIB and treatment as usual, participants in the T-SIB group who completed therapy showed a decline in NSSI behavior beginning in week 6, when alternative behaviors were first implemented (p=0.007). Small-to-medium effect sizes* were observed in this outcome every week, from week 6 through the end of treatment (range of effect sizes, 0.27–0.48). The number of NSSI days also decreased somewhat after week 7 in patients who completed T-SIB.

Discussion: Dialectical behavior therapy (DBT), developed to treat borderline personality disorder, has a focus on suicidal behaviors and NSSI and has been effective in clinical trials. Few studies have examined the effects of DBT in patients without a borderline diagnosis, and there are no established therapies in non-borderline patients. T-SIB was designed to address the limitations of DBT, with wider applicability and a shorter duration.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Andover M, Schatten H, Morris B, Holman C, et al: An intervention for nonsuicidal self-injury in young adults: a pilot randomized controlled trial. *Journal of Consulting and Clinical Psychology* 2017; doi 10.1037/ccp0000206. From Fordham University, New York, NY; and other institutions. **Funded by the NIMH. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

rTMS for Alcohol Use Disorder

In a small controlled pilot study, deep repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex (DLPFC) was associated with reductions in striatal dopamine transporter availability as well as alcohol intake in patients with alcohol use disorder.

Methods: The study enrolled 14 patients (mean age, 49 years; 12 men) seeking treatment for alcohol use disorder and 20 healthy controls, matched from a database of persons undergoing single photon emission computed tomography (SPECT) for research purposes. Patients had ≥2 days/week of excessive drinking during the month before screening and were willing to abstain or significantly reduce their alcohol consumption. Patients underwent SPECT assessment of striatal dopamine transporter activity at baseline and after 4 weeks of treatment with randomly assigned real or sham rTMS. TMS was delivered to the bilateral DLPFC using a coil that allows deeper, bilateral stimulation compared with the traditional coil. Each patient received 3 sessions per week for 4 weeks.

Results: Study participants had average scores on the Alcohol Dependence Scale indicating moderate dependence. Of the 14 patients, 3 dropped out of the study after receiving a baseline evaluation, 5 received treatment with real rTMS, and 6 received sham treatment. No adverse effects of deep rTMS were reported.

Patients who received real rTMS had statistically significant decreases in alcohol consumption from the baseline. (See table.) Those who received sham rTMS also reduced their consumption, but not by a statistically significant margin. Measurements of craving did not show a change

Mean change in alcohol consumption in patients receiving active rTMS

Alcohol Consumption	Pre-rTMS	During rTMS	Significance
Abstinence days	8	18	p=0.03
Drinking days	20	9	p=0.025
Heavy drinking days	14	7	p=0.06
Drinks per drinking day	8	3	p=0.009
Total drinks	225	75	p=0.008

from baseline in either group. State anxiety levels on the State-Trait Anxiety Inventory decreased significantly in the real rTMS group (p=0.049), but not in the sham treatment group. The groups did not differ in trait anxiety or depression.

Before treatment, patients with alcohol use disorder had higher striatal dopamine transporter activity in the right and left caudate and right and left putamen than the control subjects. Activity was not correlated with the severity and duration of alcohol dependence or with craving. After treatment, dopamine transporter activity decreased to control levels in the patients who received real rTMS, but not in those who received sham treatment.

Discussion: The dopaminergic system is known to have a role in alcohol use disorder, but it is unknown whether it is related to cause or consequence. rTMS in the DLPFC is known to increase dopamine release in the striatal pathway. The observation of decreased dopamine transporter availability in the caudate and putamen suggests deep rTMS may have actions in areas distant from the application site, strengthening the hypothesis that cortical stimulation could modulate subcortical activity.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial, but the source of funding was not disclosed.

Addolorato G, Antonelli M, Cocciolillo F, Vassallo G, et al: Deep transcranial magnetic stimulation of the dorsolateral prefrontal cortex in alcohol use disorder patients: effects on dopamine transporter availability and alcohol intake. *European Neuropsychopharmacology* 2017; doi 10.1016/j.euroneuro.2017.03.008. From the Universita Cattolica del Sacro Cuore, Rome, Italy; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

***See Reference Guide.**

ECT in Schizophrenia

According to the results of a large retrospective study, electroconvulsive therapy is clinically effective for severe, refractory schizophrenia and is associated with a low rate of cognitive impairment in this patient population.

Background: The current standard of care for schizophrenia recommends clozapine (*Clozaril*) after 2 failed trials of other antipsychotics, but there are no guidelines for treatment after clozapine failure. Although some evidence suggests that ECT may be considered, the evidence base supporting its use is limited.

Methods: Charts were reviewed for all patients referred to the ECT program at an academic psychiatric hospital over a 5-year period. Patients were included in the analysis if they had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and received ≥1 acute course of ECT. Substitute decision makers were appointed for those who lacked the capacity to consent to ECT. Electrode placement was determined by the ECT psychiatrist based on clinical variables and was generally bilateral, although some patients received standard or ultrabrief right unilateral ECT. Response was assessed by chart review using a 4-point scale, with "excellent" or "good" ratings classified as treatment response. For example, good response was characterized by chart comments indicating referral for maintenance ECT or significant reduction in severity of target symptoms. Clinical Global Impression–Improvement (CGI-I) ratings were available for about half of the treatment courses. Cognitive impairment was also rated on a 4-point scale.

Results: The study included 144 patients who received a total of 171 courses of acute ECT. The majority were hospitalized (95%), were taking antipsychotics (99%), lacked the capacity to consent to ECT (60%), were referred because of failed pharmacotherapy (73%), and received 12 sessions of bilateral ECT (86%). About half of patients were receiving clozapine during ECT.

Based on information in the charts, 77% of ECT courses resulted in a good or excellent response. Based on CGI-I ratings, 82% of patients showed clinically significant improvement. Nearly

half of patients were referred for maintenance ECT, and 45% were discharged within 31 days of ECT completion. Responders were more likely than nonresponders to have had a previous good response to ECT (p=0.017) and were less likely to be receiving antiepileptic drug therapy (p=0.007) and to have had a referral indication of failed pharmacotherapy (p=0.012). Improvement was not associated with clozapine or benzodiazepine treatment. Information about cognitive impairment was available for 89 treatment courses. Moderate or severe cognitive impairment was observed in 8 courses (9%). Of note, all patients in whom cognitive impairment developed had received ≥6 ECT sessions with bilateral electrode placement; both bilateral ECT and a greater number of treatments are known risk factors for cognitive impairment.

Discussion: Results of this study suggest ECT may be an appropriate augmentation treatment for patients who have not had adequate response to clozapine and that risk of cognitive impairment in these patients may be less concerning than in patients with depression.

Kaster T, Daskalakis Z, Blumberger D: Clinical effectiveness and cognitive impact of electroconvulsive therapy for schizophrenia: a large retrospective study. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16m10686. From the Centre for Addiction and Mental Health, Toronto; and the University of Toronto, Canada. **This study was conducted without funding. Two study authors disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

Mobile App Intervention for Depression

In a pilot study, PRIME-D, a mobile app with coaching support for treating depression, was feasible, acceptable, and effective. This type of application has the potential to increase access to mental health care with a relatively small investment of therapist time.

Background: PRIME-D, a modification of an app originally designed for patients with recent-onset schizophrenia, is a supportive online community where participants can select small health, social, or other goals and document their progress while communicating with their peers within the community. Participants are assigned a motivation coach (Master's level clinician) who uses techniques from cognitive behavioral therapy, behavioral activation, mindfulness, and psychoeducation to help them accomplish their goals. Coaches were assigned to participants in a ratio of about 1:10 and they spent an average of <2 hours per week (20 minutes per participant) coaching.

Methods: Study participants were recruited using online ads and were required to have an iPhone, to pass a quiz demonstrating understanding of informed consent, and to complete baseline assessments of depression and disability. Patient Health Questionnaire (PHQ-9) scores that indicated patients felt disabled because of their mood symptoms were required for study entry. Eligible participants (n=36; mean age, 31 years; 78% women) were instructed to use the app daily, with a minimum of once a week, for 8 weeks. Acceptability of PRIME-D was measured with satisfaction questionnaires halfway through treatment and then upon treatment completion. Feasibility was evaluated by examining usage statistics. Depression symptoms and disability were measured in-app with the PHQ-9 and the Sheehan Disability Scale.

Results: Of the 36 patients who participated in PRIME-D, 6 dropped out of the study within the first 2 weeks and the remaining 30 patients (83%) completed the program. At 8 weeks, 93% of participants indicated that PRIME-D helped them achieve their goals, a similar proportion said they would like to continue using it, and 83% said they would recommend the program to others. Participants logged in to PRIME-D an average of 4.5 days each week. They had about 3 interactions with the coach and 2 with peers each week and completed an average of 2 goal-oriented challenges per week.

Both self-reported depressive symptoms and disability showed improvement over the course of the trial. Overall, patients reported a >50% reduction in mood symptoms. Improvement in

mood was observed within the first week of use and was sustained over the 4-week post-treatment follow-up. Improvements were greatest in those who used the program more actively—i.e., those who had more interactions with coaches and peers and who posted more frequently to the community.

Discussion: Study participants were moderately depressed and disabled at baseline, typical of patients ordinarily recommended for psychotherapy or medication. An important advantage of the PRIME-D intervention over standard treatment is that patients who endorsed depressive symptoms were given immediate access to the mobile treatment, which led to rapid and robust improvement in mood. In traditional care settings, there is often a waiting period of up to 3 months before patients can access initial appointments for psychotherapy or pharmacotherapy.

Schlosser D, Campellone T, Truong B, Anguera J, et al: The feasibility, acceptability, and outcomes of PRIME-D: a novel mobile intervention for depression treatment. *Depression and Anxiety* 2017; doi 10.1002/da.22624. From the University of California, San Francisco; and other institutions. **Funded by the NIH. The authors declared no competing interests.**

New ADHD Screening Scale for Adults

A new, short, easily scored screening scale for adult ADHD has shown high predictive value in both general population and clinical samples.[1] The new scale is a revised version of the widely used Adult ADHD Self-Report Scale (ASRS), updated to reflect DSM-5 criteria.

Methods: The validation study included 3 samples: patients from the National Comorbidity Survey Replication (NCS-R) conducted in 2001–2003 (n=119); managed-care enrollees interviewed by telephone in 2004–2005 (n=218); and a clinical sample of adults obtaining a free evaluation for ADHD, assessed in 2011–2012, plus a local control group (n=300). All 3 samples were administered the full DSM-IV ASRS and a semistructured diagnostic interview based on the Adult ADHD Clinical Diagnostic Scale (ACDS). The DSM-IV ASRS was developed using 1 question for each DSM-IV criterion symptom of inattention and hyperactivity-impulsivity, plus 11 non-DSM-IV symptoms reflecting deficits in higher-level executive function. Respondents rated the recent frequency of each symptom on a 5-point scale. The DSM-5 diagnosis required 6–9 childhood symptoms and 5–9 current adult symptoms, symptom onset before age 12 years, and current functional impairment. The new screening scale was developed by applying a machine-learning algorithm to the full DSM-IV ASRS scale, plus the additional executive function items, to select the combination that best predicted the clinical diagnosis using a limited number of items and integer scoring. The scale was developed using pooled data from the NCS-R and managed-care samples and then validated in the clinical sample.

Results: Based on the clinical interview, the prevalence of DSM-5 adult ADHD was 8.2% in the pooled combination of the 2 general-population samples, weighted to reflect the general U.S. population. The development analysis for the DSM-5 screening scale resulted in a total of 6 items, some reflecting DSM-5 symptoms and others reflecting non-DSM symptoms of executive function. The items, which reflected the frequency

DSM-5 ASRS Screening Scale

DSM-5 Symptoms

1. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?

2. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?

3. How often do you have difficulty unwinding and relaxing when you have time to yourself?

4. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to before they can finish them themselves?

Non-DSM Executive Function

5. How often do you put things off until the last minute?

6. How often do you depend on others to keep your life in order and attend to details?

of occurrence in the past 6 months, produced a total score range of 0–24. Operating characteristics of the DSM-5 scale were optimal using a cutoff score of ≥14 points to identify ADHD, at which point they had a sensitivity* of 91%–92%, specificity* of 74%–96%, and positive predictive value* of 68%–83% in the clinical samples.

Discussion: The new DSM-5 ASRS screening scale showed excellent operating characteristics, correctly identifying nearly all people who met diagnostic criteria in the general population, where prevalence was low and cases were often mild, and in the clinical population where prevalences were high and symptoms were often severe. However, the scale should be considered optimal only for people with enough insight to recognize their symptoms.

Editorial.[2] This new scale raises the issue of whether current diagnostic criteria, designed with children in mind, can adequately capture the expression of ADHD in adulthood. Three of the 6 items in the DSM-5 screening scale were associated with interpersonal behaviors such as interrupting or relying on others to keep life in order. The predictive power of these items suggests it may be easier for adults to identify relationship problems than other symptoms and may reflect the importance of the effect of ADHD on relationships in adults.

[1]Ustun B, Adler L, Rudin C, Faraone S, et al: The World Health Organization adult attention-deficit/hyperactivity disorder self-report screening scale for DSM-5. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.0298. From Massachusetts Institute of Technology, Cambridge, MA; and other institutions. **Funded by Eli Lilly and Company; and other sources. Four study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

[2]Shaw P, Ahn K, Rapoport J: Good news for screening for adult attention-deficit/hyperactivity disorder [editorial]. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.0296. From the National Human Genome Research Institute; and the NIMH, Bethesda, MD. **The authors declared no competing interests.**

***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.

Positive Predictive Value: The proportion of patients with positive test results who are correctly diagnosed.

Sensitivity and Specificity: Statistical measures of the performance of binary classification tests. Sensitivity measures the proportion of actual positives that are correctly identified (i.e., the percentage of sick people who are correctly identified as having the condition). Specificity measures the proportion of negatives that are correctly identified (i.e., the percentage of healthy people who are correctly identified as not having the condition). A perfect predictor would have 100% sensitivity and specificity.

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). The rating checklists are posted at www.alertpubs.com.

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New CME activities will be released next month. Have you enrolled?

Acute Oxytocin for PTSD Prevention

In a small randomized trial, repeated intranasal oxytocin administration showed preliminary efficacy at preventing PTSD in persons with high symptom severity after a recent trauma. However, paradoxically, a single administration used in 2 neuroimaging studies increased study participants' fears.

Background: The first hours to weeks after a trauma are a suitable time period for secondary prevention of PTSD. However, >90% of patients with PTSD do not seek treatment within the first year of symptoms. Previous studies have shown no benefit of benzodiazepines, propranolol (*Inderal*), or psychological debriefing in secondary prevention. Oxytocin is a hypothalamic neuropeptide with multiple peripheral and central actions, notably anxiolytic and anti-stress effects. The effects of oxytocin administration appear to depend on context, because the hormone may enhance salience processing—i.e., increased processing of contextual cues that normally attract attention. This theory postulates that oxytocin will enhance the salience of either safety or threat signals, depending on which is present in the environment.

Single-dose administration. Two neuroimaging studies were conducted in persons who recently experienced a traumatic event. In the first, 41 trauma-exposed patients were tested with functional MRI (fMRI) during a face-matching task within 11 days of the trauma. Intranasal oxytocin administration increased amygdala reactivity to fearful faces in both genders and reactivity to neutral faces in women. In a second experiment, 37 patients underwent fMRI after listening to scripts that were either emotionally neutral or related to their recent trauma. Compared with placebo, oxytocin was associated with decreased functional connectivity between the amygdala and ventromedial and ventrolateral prefrontal cortex and with lower levels of sleepiness and higher flashback intensity. The author concluded that a single oxytocin administration may acutely impede emotional regulation in recently trauma-exposed individuals.

Repeated administration. In a subsequent clinical trial, 107 patients received 8 days of intranasal oxytocin or placebo, beginning within 12 days of a traumatic event. Overall, oxytocin did not

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affect symptoms of PTSD, depression, or anxiety, measured at intervals up to 6 months post-trauma. However, oxytocin did reduce PTSD symptoms in study participants with a high level of acute symptoms, suggesting that 8 days of intranasal oxytocin may be a promising acute intervention in highly symptomatic individuals.

Discussion: The discrepancy of findings may be explained by the salience processing theory. Patients already stressed by their recent trauma may have perceived the neuroimaging environment as unsafe or threatening, an effect that may have been enhanced by oxytocin. Administration frequency may also influence its effects; single, but not repeated, administration may enhance anxiety, a phenomenon that has been observed with SSRIs. Another possible explanation is that oxytocin may not act on PTSD symptoms by affecting amygdala function and anxiety as a primary mechanism, as hypothesized, but rather by effects on other vulnerability or etiological factors such as social support seeking behavior, or by affecting autonomic or glucocorticoid stress reactivity.

Frijling J: Preventing PTSD with oxytocin: effects of oxytocin administration on fear neurocircuitry and PTSD symptom development in recently trauma-exposed individuals. *European Journal of Psychotraumatology* 2017; doi 10.1080/20008198.2017.1302652. From the University of Amsterdam, the Netherlands. **Funded by the Academic Medical Centre Research Council of the University of Amsterdam. The author declared no competing interests.**

Efficacy of Therapies for Borderline Personality

Specific psychotherapies for borderline personality disorder are modestly superior to more general therapies, according to a meta-analysis of controlled trials.[1] However, recent improvements in the structuring of treatment-as-usual (TAU) interventions may have reduced the advantage of more focused therapies.[2]

Methods: The meta-analysis included randomized controlled trials limited to adults with borderline personality disorder, in which a specific psychotherapy was compared with a control condition—i.e., TAU or another specific therapy. Concomitant medication was not grounds for exclusion unless it was prescribed in a standardized manner by study design. Borderline-specific therapies were grouped as dialectical behavior therapy (DBT), psychodynamic therapy, cognitive behavioral therapy (CBT), and other. Effect sizes* were calculated for a range of outcomes including borderline symptoms, self-harm, and health-service use. Effects were compared immediately post-treatment and for up to 2 years of follow-up.

Results: The analysis was based on 33 trials that included 1169 patients in the active-treatment groups and 1087 controls. In 22 trials, specific psychotherapy alone was compared with TAU; in 11 trials the investigated treatment was an add-on to TAU. There were 12 trials of DBT, 8 of psychodynamic therapies, and 5 of CBT. TAU was the control treatment in 21 trials and was manualized in 10. The treatment developer was an author in 20 trials. Treatment duration ranged from 2.5 to 24 months, and the number of group or individual sessions ranged from 6 to 312.

For immediate outcomes, specific therapies had similar effects in trials with stand-alone or add-on designs. For the combined outcome of borderline symptoms, self-harm/parasuicidal behavior, and suicide, the effect size (0.35) was modest but significant. Among types of specific therapy, DBT (effect size, 0.34) and psychodynamic therapy (effect size, 0.4) were significantly more effective than control interventions, while CBT was not (effect size, 0.24). Results were not significant for the outcome of treatment retention. For the outcomes of health-service use and general psychopathology/anxiety/depression, results were varied depending on study design, but they were generally modest.

Suicide and other mortality were the only adverse effects assessed at follow-up. The total number of patient deaths was 6 in those receiving specific treatment and 6 in TAU patients;

suicide-related deaths occurred in 2 and 5 patients, respectively. The difference in long-term effects on the combined outcome measure was statistically significant, but results were highly heterogeneous and did not remain significant after correction for publication bias. In general, studies with a lower risk of bias were less likely to show a difference between specific therapies and TAU.

Discussion: The modest effect sizes for disorder-specific therapies may be due in part to TAU patients benefitting from special attention and from having a manualized, structured treatment. It is also possible that outcomes may be better in TAU groups in recent trials because TAU itself has improved.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

[1]Cristea I, Gentili C, Cotet C, Palomba D, et al: Efficacy of psychotherapies for borderline personality disorder: a systematic review and meta-analysis. *JAMA Psychiatry* 2017;74 (April):319–328. From Babes-Bolyai University, Romania; and other institutions. **Funded by the Romanian National Authority for Scientific Research and Innovation; and the University of Padova, Italy. The authors declared no competing interests.**

[2]Fonagy P, Luyten P, Bateman A: Treating borderline personality disorder with psychotherapy: where do we go from here [editorial]? *JAMA Psychiatry* 2017;74 (April):316–317. From University College London, U.K.; and other institutions. **All study authors disclosed financial relationships with commercial sources.**

***See Reference Guide.**

Cannabis in Tourette Syndrome

Preliminary evidence from a retrospective chart review suggests that cannabis may improve symptoms of Tourette syndrome, as well as common comorbidities. The review suggests effects of inhaled cannabis may be greater than those reported with oral formulations of THC or other cannabinoids.

Methods: Records from a Tourette syndrome clinic were reviewed to identify patients who had used cannabis regularly for ≥6 months. Of 21 patients identified, 19 agreed to participate in the study by completing in-person interviews. Baseline symptom severity was assessed using the Yale Global Tic Severity Scale (YGTSS), based on retrospective chart data and patient recollection. The primary efficacy endpoints were change from baseline in the YGTSS score and the percentage of patients who had a Clinical Global Impression–Improvement (CGI-I) rating of much improved or very much improved. Adverse events were assessed using the Marijuana Effect Expectancy Questionnaire (MEEQ).

Results: The 19 patients (mean age, 32 years; 16 men) had been using cannabis regularly for ≥2 years. All but 1 had previously received treatment for their tics with clonidine (*Catapres*) and/or antipsychotics. Nearly half had previously participated in clinical trials of oral pharmaceutical cannabinoids. The patients reported that these cannabinoids had been helpful, but not as effective as inhaled cannabis.

Patients obtained their cannabis from approved or unapproved suppliers and all but 1 administered it by smoking or vaporized inhalation. Eight of the patients serendipitously discovered that marijuana improved their tics after recreational use. It was impossible to determine the cannabis dosage or THC/cannabinoid content. Patients used cannabis at frequencies ranging from multiple times a day to twice weekly. One patient smoked daily for a week and then refrained for 3 weeks. The tic-reducing effect typically lasted about 3 hours, but in a few cases it lasted up to 12 hours.

All patients had clinically significant symptom relief evidenced by an average reduction of 60% in YGTSS total tic severity from a baseline mean of 31 to 12 ($p<0.001$). Comparably large reductions were seen on the YGTSS motor and vocal tic severity subscales and on the impairment subscale ($p<0.001$ for all). Among the 13 patients with a comorbid diagnosis of obsessive-

compulsive disorder, average scores on the Yale-Brown Obsessive Compulsive Scale decreased by about 50% (p=0.001). Of the 13 patients who also met Adult ADHD Self-Report Scale criteria for ADHD, only 1 continued to meet the criteria while using cannabis. A total of 18 patients had CGI-I ratings of much or very much improved during cannabis use.

Patients reported low rates of adverse effects on the MEEQ. In response to open-ended questions, some (≤3 each) reported feeling high, impaired concentration or memory, increased appetite, or other typical marijuana effects. One patient initially experienced irritability, but was able to control this effect by reducing the frequency of use.

Discussion: The large improvement observed in these patients may be due to the uncontrolled nature of this study. However, it is noteworthy that many did not respond as robustly to trials of oral or oromucosal formulations of THC or cannabidiol. Anti-tic effects of medical marijuana may be enhanced by other compounds it contains or by an administration route that avoids first-pass hepatic metabolism. In addition, limited information suggests that inhalation may deliver much higher doses of THC than oral administration.

Abi-Jaoude E, Chen L, Cheung P, Bhikram T, et al: Preliminary evidence on cannabis effectiveness and tolerability for adults with Tourette syndrome. *Journal of Neuropsychiatry & Clinical Neurosciences* 2017; doi 10.1176/appi.neuropsych.16110310. From the University of Toronto, Canada; and other institutions including AstraZeneca Inc., Mississauga, Canada. **Funded by the Toronto General & Western Hospital Foundation; and other sources. Two of 5 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Supplementary CBT for Drug-Resistant Depression

In a randomized controlled trial, adding cognitive behavioral therapy to antidepressant medication was effective in patients with pharmacotherapy-resistant depression.[1]

Methods: The study was conducted in patients seeking treatment for major depressive disorder (single or multiple episodes), who had at least a minimal degree of treatment resistance despite ≥8 weeks of adequate medication. Resistance was measured according to the Maudsley Staging Method, which incorporates the number of failed antidepressant trials, augmentation strategies, and ECT, as well as depression severity and episode duration. Patients (n=80) were randomly assigned to receive treatment as usual, either with or without CBT. The CBT protocol was designed according to a standard manual and was delivered in 16 individual weekly sessions, with up to 4 additional sessions if needed. Treatment as usual consisted of brief bi-weekly visits providing medication management, education, and supportive guidance. The primary study outcome measure was a modified version of the 17-item Hamilton Rating Scale for Depression (HAM-D). Outcomes were rated by evaluators blinded to patients' treatment assignment.

Results: At study entry, treatment resistance was classified as moderate in nearly 70% of patients. About 20% of participants had a history of psychiatric hospitalization or suicide attempts. The majority of patients (>60%) had received ≥3 antidepressant trials, and nearly half were receiving ≥2 medications at randomization. All but 1 patient assigned to CBT completed the study. Antidepressant dosage did not differ between the 2 groups during the 16 weeks of CBT.

Depressive symptoms decreased in both treatment groups, but the mean improvement in HAM-D score was significantly larger with CBT (12.7 vs. 7.4 with treatment as usual; p<0.001). CBT remained significantly more effective at 3, 6, and 12 months of follow-up. Patients who received supplemental CBT were twice as likely as controls to experience response and remission (see table, next page), and this advantage was also maintained at most time points throughout the year of follow-up. However, the 2 groups did not differ with regard to self-reported secondary measures of depression, the Beck Depression Inventory and the Quick Inventory for Depressive Symptomatology; nor did they report different outcomes on the Short Form-36 measure of health-related quality of life.

Response and remission at 16 weeks					
	CBT	Treatment as usual	Relative risk*	Significance	Number needed to treat*
Response†	31 (78%)	13 (33%)	2.38	p<0.001	5
Remission††	17 (43%)	8 (20%)	2.13	p=0.03	5

†≥50% reduction in modified HAM-D
††Final HAM-D ≤7

None of the participants experienced serious adverse events during the intervention period. During follow-up, 1 patient in the treatment-as-usual group was hospitalized for depression and another committed suicide.

Discussion: These results confirm and extend previous observations from another large-scale study in primary care patients,[2] but conflict with outcomes of the STAR*D trial,[3] which was conducted in both psychiatric and primary care patients. Several aspects of STAR*D may have dampened patients' enthusiasm for CBT; specifically, those randomized to CBT were allowed to decline the option and had to pay if they received it. In the present study, patient biases in describing symptoms may partially account for the lack of effect on self-report measures.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

[1]Nakagawa A, Mitsuda D, Sado M, Abe T, et al: Effectiveness of supplementary cognitive-behavioral therapy for pharmacotherapy-resistant depression: a randomized controlled trial. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.15m10511. From Keio University School of Medicine, Tokyo, Japan; and other institutions. **Funded by the Japanese Ministry of Health, Labour, and Welfare. Two of 9 authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Wiles N, et al: Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial. *Lancet* 2013;381:375–384.

[3]Trivedi M, et al: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *American Journal of Psychiatry* 2006;163:28–40.

***See Reference Guide.**

fMRI Marker for Selecting Depression Treatment

A functional MRI (fMRI) marker successfully predicted patients' differential response to antidepressant medication or cognitive behavioral therapy (CBT). The marker identified patients most likely to achieve remission and those most likely to have treatment failure with each of the 2 options.

Methods: Study participants were adults with a primary current diagnosis of major depressive disorder, a score of ≥18 on the 17-item Hamilton Rating Scale for Depression (HAM-D), and no history of adequate treatment with an antidepressant drug or evidence-based psychotherapy. Patients were randomly assigned to 12 weeks of treatment with either an SSRI (10–20 mg/day escitalopram), an SNRI (30–60 mg/day duloxetine), or manualized CBT. Remission was defined as a HAM-D score of ≤7 at study weeks 10 and 12. Treatment failure was defined as <30% reduction in the HAM-D from baseline to week 12.

Before randomization, study participants underwent a resting-state fMRI. Analysis was conducted to assess the functional connectivity of the subcallosal cingulate cortex (SCC), a region of the limbic system that modulates emotional behavior and is involved in feelings of sadness. Data from patients who met the extremes of outcome—either remission or treatment failure—was used to screen for a pattern that might predict these outcomes.

Results: Of 234 patients who completed randomized treatment, 122 had adequate fMRIs for analysis. A total of 82 patients had clear clinical outcomes, either remission (n=58) or treatment failure (n=24). Differential response to medication or CBT was predicted by SCC connectivity with 6 brain regions. This number was reduced to 3 by further statistical analysis to reduce the impact of outliers. These regions were the left midbrain, left frontal operculum, and the left ventromedial prefrontal cortex. For each of these regions, greater functional connectivity with the SCC was associated with remission in patients who received CBT and with failure of medication, while reduced connectivity was associated with the opposite pattern. Results did not differ in separate analyses for each of the 2 drugs.

In an analysis of summed connectivity scores for the 3 relevant regions, 78% of CBT remitters versus nonremitters were correctly identified, as were 89% of treatment failures versus non-failures. For medication, these rates were 72% for remission and 75% for treatment failure. The connectivity subgroups did not differ on any clinical or demographic characteristic, which suggests SCC connectivity is not a marker for something more easily measured.

Discussion: These results suggest that positive connectivity in the left midbrain, left frontal operculum, and the left ventromedial prefrontal cortex should lead to a recommendation for CBT and negative connectivity to a recommendation for medication. If these findings are replicated, the brain-based marker could be incorporated as part of a multivariate approach to treatment selection.

Dunlop B, Rajendra J, Craighead W, Kelley M, et al: Functional connectivity of the subcallosal cingulate cortex and differential outcomes to treatment with cognitive-behavioral therapy or antidepressant medication for major depressive disorder. *American Journal of Psychiatry* 2017;174 (June):533–545. From Emory University, Atlanta, GA; and other institutions. **Funded by the NIH. Four of 9 authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names*: duloxetine—*Cymbalta*; escitalopram—*Lexapro

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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.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) 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). The rating checklists are posted at www.alertpubs.com.

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Comorbidity of Cannabis Use and Depression

Analysis of a comprehensive set of statistical models of comorbidity in twin pairs suggests that the comorbidity of major depressive disorder (MDD) and cannabis use disorder (CUD) probably proceeds in the direction of CUD causing MDD. The models suggest that risk factors for CUD may also increase risk for MDD, but perhaps only in higher risk individuals.

Background: Neale and Kendler's 13 comorbidity models (NK13) are a set of statistical models based on different assumptions about the etiological links between 2 comorbid conditions. The models fall into 4 groups: single liability (both could be alternative forms of the same disorder); independent liability (comorbidity is entirely related to a third disorder); multiformity (risk factors are related, but only after a certain threshold is reached for 1 or both disorders); and correlated liabilities (disorders are related continuously and etiological factors overlap, whether this is due to shared risk factors or causality). The latter 2 categories also contain several submodels based on thresholds and causal directions; 1 sub-model covers the possibility that comorbidity occurs in a population by chance.

Methods: The NK13 models were tested using data from participants born between 1972 and 1979 and enrolled in the Australian Twin Registry. Participants were interviewed using the Semi-Structured Assessment of the Genetics of Alcoholism, a questionnaire that assesses symptoms over a range of mental health and substance use disorders. DSM-5 criteria, modified somewhat in the case of CUD, were applied to identify the 2 disorders.

Results: Of the 2410 individuals enrolled, 15% met criteria for lifetime CUD and 26% for lifetime MDD. CUD was more common in persons with lifetime MDD than without (24% vs 12%, respectively; adjusted odds ratio,* 2.66). In monozygotic twin pairs discordant for CUD, the twins with CUD had nearly 3 times the likelihood of MDD as the twins without CUD (46% vs 28%; adjusted odds ratio, 2.83).

When the 13 statistical models were applied, 5 were rejected as a poor fit, including a chance association, alternate forms of a single disorder, and causation by a third disorder. Of the

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remaining models, 2 showed the best fit. The random multiformity model of CUD proposes that being over a threshold of CUD risk leads to an increase of risk for symptoms of MDD, even in individuals who remain below the risk threshold for MDD. The CUD-causes-MDD model proposes that liability for CUD has a causal influence on liability for MDD. According to these 2 models, 79–80% of the total variance in CUD is explained by genetic factors and the rest by non-shared environmental factors. For MDD, 43–48% of the variance is explained by genetic factors.

Discussion: Both of the best-fitting models suggest that the direction of effect goes from CUD to MDD. Their main difference is that risk increases continuously in 1 and after a threshold is crossed in the other. Another important difference is that 1 model assumes CUD causes MDD, while the other does not assume a causal direction. However, the 2 models are not incompatible. Their interpretation is supported by research findings such as the negative effect of heavy cannabis use on daily functioning, its effect on educational attainment, effects on brain structure and function, and the role of the endocannabinoid system in mood regulation.

Smolkina M, Morley K, Rijsdijk F, Agrawal A, et al: Cannabis and depression: a twin model approach to co-morbidity. *Behavioral Genetics* 2017; doi 10.1007/s10519-017-9848-0. From King's College London, U.K.; and other institutions.
Funded by the National Institute on Drug Abuse; and other sources. The authors declared no competing interests.

***See Reference Guide.**

NAC Augmentation for Resistant OCD

In a placebo-controlled trial, augmentation of ongoing medications with *N*-acetylcysteine was not more effective than placebo in treatment-resistant obsessive-compulsive disorder. NAC did however reduce patients' anxiety symptoms.

Background: The potential of NAC for treating OCD is based on its glutamate-modulating properties. Several previous small controlled trials of NAC in OCD have had mixed results.

Methods: Study participants had a primary diagnosis of OCD (DSM-IV) and a history of nonresponse to ≥1 previous medication trial lasting ≥12 weeks at an adequate dosage. Patients were required to have baseline Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores of ≥16 (or ≥10 if only affected by compulsions) and Clinical Global Impression–Severity ratings indicating at least moderate severity. Participants were randomly assigned to double-blind adjunctive treatment with either NAC or placebo. Ongoing medications were continued at a stable dosage throughout the randomized trial. NAC was administered at an escalating dosage to a maximum of 3000 mg/day after 2 weeks. The primary efficacy outcome was change from baseline in the Y-BOCS total score after 16 weeks of study treatment.

Results: Of the 39 patients who began treatment with NAC or placebo, 35 completed the trial. At baseline, the mean total Y-BOCS score was 25.2 and reductions averaged 4.3 points with NAC and 3.0 points with placebo, a nonsignificant difference. The groups did not differ in average reductions in either obsessive or compulsive symptom subscales or in the number of responders (i.e., ≥25% reduction in Y-BOCS score): 6 patients with NAC and 5 with placebo.

A wide range of secondary outcomes, including measures of global improvement, depression, and specific OCD symptom domains, did not differ between NAC and placebo. Only mean reductions in scores on the Beck Anxiety Inventory were significantly larger with NAC than with placebo (p=0.02).

Discussion: Previous trials that showed benefits of NAC in OCD had a shorter treatment duration and used lower doses. In addition, subjects in the present study had highly-resistant

disease (average of 3.4 previous failed treatment trials) and only 1 had specific behaviors related to sensory phenomenon. The potential benefits of NAC augmentation in a less severely refractory sample and in those with sensory phenomenon cannot be ruled out.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Costa D, Diniz J, Requena G, Joaquim M, et al: Randomized, double-blind, placebo-controlled trial of *N*-acetylcysteine augmentation for treatment-resistant obsessive-compulsive disorder. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16m11101. From the University of Sao Paulo Medical School, Brazil; and Yale University, New Haven, CT. **Funded by the Foundation for Research Support in the State of Sao Paulo. The study authors declared no competing interests.**

***See Reference Guide.**

Potential Treatment Target in Schizophrenia

Levels of kynurenic acid (KYNA), an endogenous glutamate receptor antagonist, are increased in the CNS of patients with schizophrenia, according to a meta-analysis. This research supports the glutamatergic hypothesis of schizophrenia, an alternative or coexisting mechanism to the hypothesis of dopamine dysregulation.

Background: The dopamine hypothesis does not explain the negative and cognitive symptoms of schizophrenia or why up to one-third of patients do not experience response with antipsychotics, which act mainly through dopamine receptor antagonism. Research has shown that administration of NMDA receptor (NMDAR) antagonists leads to the emergence of positive, negative, and cognitive symptoms, supporting the glutamatergic hypothesis. It has been proposed that hypofunctioning NMDARs are involved in schizophrenia. KYNA is the only known endogenous NMDAR antagonist. It is produced as part of the metabolic pathway of tryptophan. Its precursor, kynurenine (KYN), readily crosses the blood-brain barrier and is converted to KYNA in the brain, primarily within astrocytes. KYNA levels have been measured in various studies of patients with schizophrenia. The aim of this meta-analysis was to examine more closely the difference in KYNA levels between patients and healthy controls.

Methods: A comprehensive literature search identified 13 eligible studies with a total of 961 subjects with schizophrenia in whom KYNA levels were assessed. Patients had an average age of 38 years, two-thirds were men, and about two-thirds were receiving antipsychotic medication. Four studies measured KYNA in cerebrospinal fluid, 3 in brain tissue, 5 in plasma or serum, and 1 in saliva.

Results: Overall, KYNA levels were moderately higher in patients with schizophrenia than in healthy controls (standardized mean difference [SMD],* 0.66; $p<0.00001$). KYNA levels were moderately elevated in the 7 studies measuring KYNA centrally (SMD, 0.61; $p<0.00001$) but not in those measuring KYNA in peripheral tissues. KYNA levels were higher, relative to healthy controls, in the studies with higher average patient ages, higher proportions of male patients, and higher proportions of patients receiving antipsychotics.

Discussion: The finding of an age-related increase in the difference between patients with schizophrenia and controls suggests that increasing KYNA levels may explain cognitive deterioration with age. However, not all studies have found an association of increasing age with KYNA levels. The finding of a positive association of KYNA with antipsychotic medication status is in contrast with previous research that suggested antipsychotic medication reduced KYNA levels.

It has been suggested that KYNA levels are elevated in schizophrenia because of increased availability of the precursor KYN, owing to peripheral inflammatory processes. Alterations in brain enzymes or astrocyte activation are additional possible explanations. Several

approaches have been explored to manipulate KYNA levels in animals and humans, including NMDAR agonists, COX-1 and COX-2 inhibitors, and tryptophan depletion. These manipulations have had mixed clinical effects.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Plitman E, Iwata Y, Caravaggio F, Nakasima S, et al: Kynurenic acid in schizophrenia: a systematic review and meta-analysis. *Schizophrenia Bulletin* 2017;43 (July):764–777. From the Centre for Addiction and Mental Health, Toronto, Canada; and other institutions. **Funded by a Vanier Canada Graduate Scholarship; and the Canadian Institute of Health Research. Five of 11 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Swallowing Disorders in Schizophrenia

In patients with schizophrenia, swallowing disorders are common and may be an important but unrecognized source of morbidity and mortality. These disorders have not been well characterized, but according to a review, the few existing studies indicate that patients with schizophrenia have elevated rates of dysphagia and deaths from asphyxia, the latter due to choking on food. Mortality and morbidity are generally related to either acute asphyxia from airway obstruction or aspiration pneumonia.

Swallowing disorders in schizophrenia may be either drug- or illness-related. Drug-related disorders have been better studied and are mostly associated with extrapyramidal effects of antipsychotic medications. Illness-related disorders are generally associated with behaviors such as rapid eating and ingesting large boluses of unchewed food.

Drug-induced parkinsonism may cause poor tongue movement, impaired bolus formation and control, and changes in the pharyngeal phase of swallowing. Both first- and second-generation antipsychotics have been reported to cause dysphagia related to parkinsonism. Treatment usually involves either switching to another drug with less extensive dopamine blockade or treatment with an anticholinergic agent or amantadine (*Symmetrel*). If problems persist, modifications used in Parkinson's disease can be introduced—e.g., chin tucks, taking smaller bites, and ingesting thickened liquids. Dystonic reactions are a serious early complication of first-generation and, rarely, second-generation antipsychotics. These reactions require urgent treatment with parenteral anticholinergics, or if laryngospasm occurs, intubation. Dysphagia related to tardive dyskinesia is more difficult to treat. Discontinuing or switching the antipsychotic may result in improvement within 3 months.

In addition to extrapyramidal symptoms, antipsychotic drugs may induce dry mouth via anticholinergic effects. In addition to affecting bolus formation and swallowing, anticholinergic medications may also inhibit esophageal peristalsis. Sedating drugs can inhibit the gag reflex, increasing choking and aspiration risk. Most medications can cause allergic reactions and angioedema that can impair swallowing.

Abnormal swallowing and eating behavior may be a greater influence than drugs in aspiration, choking, and asphyxia. Schizophrenia is associated with rapid eating, intake of large boluses of food (sometimes discovered on autopsy of choking victims), swallowing of unchewed food or nonfood items, pocketing of food in the mouth, distraction during meals, and possibly inherent changes in swallowing physiology. There is no data regarding whether these problems respond to treatment of the underlying schizophrenia. Behavioral interventions have been reported to be helpful, generally in more severely ill, institutionalized patients. These include staff education, mealtime supervision, dietary modification, and training by the speech pathologist. Patients may be trained to take smaller bites, chew

their food, and put the utensils down between bites; however, many patients may not remember or comply with these instructions. Passive interventions include smaller utensils and finely cut food.

Kulkarni D, Kamath V, Stewart J: Swallowing disorders in schizophrenia. *Dysphagia* 2017; doi 10.1007/s00455-017-9802-6. From the University of South Florida, Tampa; and other institutions. **This review was not funded. The authors declared no competing interests.**

Xenon for Panic Disorder

In an open-label pilot study, xenon inhalation for 6 or 7 brief sessions resulted in a marked, long-term reduction in panic-disorder symptoms.

Background: Xenon is an inert gas with neuroprotective/anesthetic properties. It has no toxicity and, unlike ketamine, no psychotomimetic effects. Other advantages include cardiovascular stability and rapid induction. It can also be administered safely in an outpatient setting with minimal monitoring.

Methods: The study, conducted in Russia, enrolled 90 outpatients with panic disorder. Xenon was administered as monotherapy in the study patients with isolated panic disorder; in the patients with comorbid conditions, xenon was added to their ongoing therapy, which mainly consisted of SSRIs or SNRIs for depression. Xenon was administered daily for 3 days, and then every other day for a total of 6 or 7 sessions. Medical-grade xenon was mixed with oxygen—first in a 15%/85% ratio, and then escalated to 30%/70%—and inhaled via face mask for 2.5–4 minutes until a total xenon intake of 3.0 L was reached. Treatment outcome was assessed after each xenon inhalation and 30 and 180 days after the end of treatment.

Results: Patients had a mean age of 35 years and had been experiencing panic disorder for >1 year. In the comorbid group, the most frequent other diagnoses were mixed anxiety/depression (44%), bipolar disorder (10%), and recurrent depression (10%). Five patients withdrew from the study because of minor adverse effects (i.e., dizziness and headache), and an additional 4 for other reasons, leaving 81 (42 patients with isolated panic disorder and 39 with comorbid conditions) included in this preliminary analysis.

Mean baseline scores on the Hospital Anxiety and Depression Scale (HADS; 17.7 and 19 in the isolated and comorbid groups, respectively) indicated clinically severe anxiety. After 3 sessions, the mean score had decreased to 13.3 in both groups. After 6 sessions, scores in both groups were reduced to the normal range and remained normal throughout follow-up. Clinical Global Impression (CGI)–Improvement ratings for anxiety showed marked improvement at the end of treatment in 41% of patients with isolated panic disorder and in 10% of the comorbid group. After 6 sessions, 52% and 13% of the groups, respectively, were rated as very much improved. At baseline, CGI–Severity ratings indicated severe illness. After session 3, nearly 50% of the isolated panic disorder group and 12% of the comorbid group were rated as moderately ill. CGI–Severity ratings were normal or borderline after 6 sessions in 82% of patients with isolated panic disorder and in 100% of those with comorbid disorders. Six months after treatment, no patients were experiencing major panic attacks and only a few had minor attacks. Self-reported anxiety measures showed a similar pattern. Ratings on the HADS depression subscale also showed improvement in both clinical groups.

Xenon was well tolerated by patients who competed the trial. However, 4 of the 5 patients who withdrew from the study were subsequently found to have evidence of mild vascular brain disease; their symptoms might have been the result of xenon-induced increases in vascular blood flow.

Discussion: SSRIs, SNRIs, and benzodiazepines have proven efficacy in the treatment of panic disorder, but delayed onset of action and adverse effects may limit their use. Although preliminary and requiring replication, these study results suggest that xenon may be a viable option for rapid reduction of panic disorder symptoms.

Dobrovolsky A, Ichim T, Ma D, Keasri S, et al: Xenon in the treatment of panic disorder: an open label study. *Journal of Translational Medicine* 2017; doi 10.1186/s12967–017–1237–1. From the Pirogov Russian National Medical Research University, Moscow. **Funded by Nobilis Therapeutics Inc. Three of 5 study authors disclosed financial relationships with Nobilis Therapeutics; the remaining authors declared no competing interests.**

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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.

Standardized Mean Difference: The difference between 2 normalized means—i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

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). The rating checklists are posted at www.alertpubs.com.

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PSYCHIATRY ALERTS NOS

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SAMe for Neuropsychiatric Disorders

According to a review by the Work Group of the American Psychiatric Association Council on Research, limited evidence suggests S-adenosylmethionine may be effective and its risks compare favorably with prescription antidepressants.[1] SAMe also has potential for treating neurocognitive disorders, psychotic disorders, and concomitant medical illnesses in patients with depression. However, direct comparisons with newer antidepressant agents are lacking.

SAMe is an endogenous intracellular amino acid metabolite and enzyme cosubstrate involved in multiple pathways, including biosynthesis of hormones and neurotransmitters. Normal ranges have been established, and SAMe deficiency has been observed in patients with depression, Alzheimer's disease, Parkinson's disease, and HIV infection. Orally or parenterally administered SAMe crosses the blood-brain barrier. It has been used as a treatment in Europe for >30 years and has long been available in the U.S. as an over-the-counter supplement.

There have been >50 clinical trials of SAMe for depression, including 19 placebo-controlled trials and 21 trials comparing SAMe with prescription antidepressants. Early trials reported SAMe-induced mania or hypomania emergence, had inconsistent diagnostic criteria for depression, and used parenteral administration. Oral dosage forms became available in the 1980s. A seminal meta-analysis of the antidepressant effects of SAMe,[2] conducted in 2002, remains relevant because there has been little subsequent research. The meta-analysis found that SAMe was more effective than placebo at treating depression, with an overall effect size* of 0.65. This effect size corresponds to a 5–6-point improvement on the Hamilton Rating Scale for Depression (HAM-D) score, generally considered a clinically significant margin; however, because of the studies' heterogeneity, the authors of the meta-analysis urged cautious interpretation of the effect size. Multiple studies have found SAMe to be as effective as tricyclic antidepressants, but again, results should be interpreted cautiously because of the studies' lack of placebo-control groups. Studies of adjunctive SAMe have generally been positive. A recently completed, multicenter, placebo-controlled add-on study showed no benefit overall, but a post-hoc analysis found adjunctive SAMe to reduce depressive symptoms in a responsive subset of patients.

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Preliminary studies suggest SAMe may be beneficial in patients with depression and comorbid conditions including HIV, Parkinson's disease, and osteoarthritis or fibromyalgia. In 1 study in men receiving treatment with other antidepressants, adjunctive SAMe was associated with lower rates of arousal dysfunction and erectile dysfunction. Preliminary studies indicate SAMe may have beneficial effects on memory-related cognition in patients with depression. A multicomponent nutraceutical containing SAMe has shown promising effects on cognition in patients with Alzheimer's disease. SAMe may ameliorate symptoms of hepatic disease in patients with comorbid depression and alcohol dependence. SAMe has been investigated for managing aggression associated with psychosis, with unclear results.

The most common adverse effect of SAMe is nausea; diarrhea, abdominal discomfort, and vomiting occur less frequently. Agitation, anxiety, and insomnia have been reported in patients sensitive to the activating effects of SAMe. As with prescription antidepressant medications, SAMe has been associated with hypomania and mania in patients with bipolar disorder. Potential benefits of SAMe relative to antidepressants may include its lack of weight gain, sexual dysfunction, and cognitive or memory dysfunction. In addition, it has few known adverse interactions with other drugs and may improve liver function in patients with medication-induced liver dysfunction.

[1]Sharma A, Gerbarg P, Bottiglieri T, Massoumil L, et al: S-adenosylmethionine (SAMe) for neuropsychiatric disorders: a clinician-oriented review of research. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16r11113. From the University of Pennsylvania, Philadelphia; and other institutions. **This review was conducted without funding. Six of 9 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Hardy M, et al. S-Adenosyl-L-Methionine (SAMe) for Treatment of Depression, Osteoarthritis, and Liver Disease: summary. Rockville, MD: Agency for Healthcare Research and Quality, US Department of Health and Human Services; 2002.

***See Reference Guide.**

Consensus Recommendations on rTMS for Depression

Repetitive transcranial magnetic stimulation has become a mainstream therapy for depression, but clinicians face a confusing array of options regarding its use, according to a task force created by the National Network of Depression Centers and the American Psychiatric Association. A consensus statement released by the workgroup summarizes the evidence in the literature and provides expert opinion where needed.

Five TMS devices are now approved by the FDA, and many state and commercial insurers cover the treatment for patients with major depressive disorder. The efficacy of rTMS is supported by extensive clinical research. The consensus recommendations are based on 118 published reports including 3 large, multicenter, randomized controlled trials, as well as many meta-analyses and systematic reviews of smaller sham-controlled trials. According to a systematic review and meta-analysis, rTMS delivered to the dorsolateral prefrontal cortex (DLPFC) is associated with an odds ratio* of 3.3 for both response and for remission. Numbers needed to treat* for response and remission are 6 and 8, respectively. The effect size* for rTMS is in the medium range. The expert consensus is that rTMS is appropriate in patients with major depression, including those with medication resistance or significant comorbid anxiety, but not in those with comorbid psychotic symptoms or acute suicidal ideation. The consensus statement offers 9 specific recommendations for clinical application of rTMS.

1. The clinical environment should include adequate space for the TMS device, the patient, and the TMS operator, who must be able to directly observe the patient. Room temperature should be sufficiently cool to prevent device overheating. All individuals present in the treatment room should wear noise-reducing earplugs. Patients undergoing treatment should remain awake and still.

2. Required operator qualifications vary by practice, but at a minimum, the TMS operator should be both trained and certified in device operation, coil targeting, and recognition and management of adverse effects including seizure.

3. Medical records of patients undergoing TMS should include the indication for treatment, device and coil types, treatment phase, cortical targets, motor threshold, treatment intensity, frequency, stimulus duration, intertrain interval, and number of stimuli. Treatment-related adverse effects and medication usage should also be noted.

4. Strong evidence supports use of H1 and figure-of-eight coils. While other coil types exist, they are not presently recommended for use in depression.

5. Most evidence for the figure-of-eight coil supports left DLPFC targets, while a smaller evidence base suggests targeting the right DLPFC. H1 coils have supporting evidence for bilateral targeting of the prefrontal cortex.

6. There are multiple methods for positioning TMS coils over targeted areas. Taking head measurements for identification of F3 using 10–20 EEG coordinates may be the most practical method in terms of time and accuracy.

7. Individual motor threshold determinations should be made before beginning the initial TMS session, and should be rechecked if the patient reports new-onset sleep disturbance or a significant change in sleep pattern.

8. Careful assessment of the risk–benefit ratio of adverse effects to likelihood of clinical response and/or remission should direct determinations on the number of treatment sessions to be included in the acute TMS course.

9. Although it is possible that psychotropic medications could affect the motor threshold, there are no absolute medication contraindications in patients undergoing TMS. However, all medications and any changes made to them should be documented.

McClintock S, Reti I, Carpenter L, McDonald W, et al: Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16cs10905. From the University of Texas Southwestern Medical Center, Dallas; and other institutions. **This consensus statement was created with no outside funding. All study authors disclosed financial relationships with commercial sources.**

***See Reference Guide.**

Telephone Therapy for Late-Life GAD

According to follow-up data from a randomized trial, telephone-delivered cognitive behavioral therapy (CBT-T) has lasting benefit in older adults with generalized anxiety disorder.[1]

Background: In a previous report,[2] the study authors showed that CBT-T was superior to telephone-delivered nondirective supportive therapy (NST-T) immediately upon completing treatment, with significantly larger improvements in worry, GAD symptoms, and depressive symptoms. The present study evaluates outcomes 1 year after treatment completion.

Methods: Participants were recruited by a direct mailing to adults aged ≥60 years living in rural North Carolina and meeting DSM-IV criteria for primary or co-primary GAD. Potential subjects were excluded if they had alcohol or substance abuse, cognitive impairment, or substantial hearing loss. Of the 141 eligible participants, 82% were women, 91% were white, and 45% had a college degree. About one-third had a current comorbid depression diagnosis, and half a comorbid anxiety diagnosis. CBT-T comprised 11 weekly sessions covering standard components of CBT, including behavioral activation and exposure therapy, with 2 optional sessions focused on pain and sleep for patients experiencing these problems. NST-T consisted of 10 weekly telephone sessions establishing a high-quality therapeutic relationship, with

reflective listening and supportive statements but no other techniques to process emotions. Both treatments were manualized and delivered by the same therapists. The primary study outcomes were anxiety symptoms, assessed with the Hamilton Rating Scale for Anxiety (HAM-A), and worry, assessed with the Penn State Worry Questionnaire-Abbreviated (PSWQ-A). Secondary outcome measures included the GAD-7, a self-reported measure of DSM-IV GAD symptoms, and the Beck Depression Inventory (BDI).

Results: At baseline, participants had a mean HAM-A score of 21, indicating moderate anxiety, and a mean PSWQ-A worry score of 31, indicating moderate-to-high worry. At 15-month follow-up, both groups demonstrated a significant decline in HAM-A score, averaging 7.6 points for CBT-T and 4.3 points for NST-T. The difference between groups was significant in favor of CBT-T (p=0.024; effect size,* 0.43). Worry scores on the PSWQ-A showed a similar pattern, with an 11-point decline for CBT-T and an 8-point decline for NST-T, and a difference of 3.13 points (p=0.016; effect size, 0.56). Both groups showed a similar and significant decline in depressive symptoms on the BDI and in GAD-7 scores (effect sizes, 0.32 and 0.38, respectively).

Response, defined as a ≥5.5-point reduction in PSWQ-A score, occurred in 86% of the CBT-T group and 66% of the NST-T group (p=0.0172). Rates of HAM-A response (≥50% decrease in score) were higher with CBT-T than with NST-T (40% vs 27%), but the between-group difference was not significant. However, the rate of remission (HAM-A score ≤7) was significantly greater with CBT-T (31% vs 15%; p=0.0397).

Discussion: A substantial portion of patients with GAD do not receive treatment, many because of difficulties accessing therapy. This may be particularly problematic for older adults and those living in rural areas. Results of the present study indicate that telephone-delivered CBT has positive and long-lasting effects in this patient population. However, because the study population was predominantly white and female, the results may not generalize to other elderly populations; the results need to be replicated in a broader sample.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

[1]Brenes G, Danhauer S, Lyles M, Anderson A, et al: Long-term effects of telephone-delivered psychotherapy for late-life GAD. *American Journal of Geriatric Psychiatry* 2017; doi 10.1016/j.jagp.2017.05.013. From Wake Forest School of Medicine, Winston-Salem, NC. **Funded by the NIMH. The authors declared no competing interests.**

[2]Brenes G, et al: Telephone-delivered cognitive behavioral therapy and telephone-delivered nondirective supportive therapy for rural older adults with generalized anxiety disorder: a randomized clinical trial. *JAMA Psychiatry* 2015;72:1012–1020.

***See Reference Guide.**

Direct Current Brain Stimulation for Depression

In a randomized controlled trial, transcranial direct current stimulation (tDCS) did not meet criteria for noninferiority to escitalopram (*Lexapro*) in patients with unipolar major depression.[1] tDCS was superior to placebo and similar to escitalopram for some secondary outcomes, but it was associated with more adverse events including new-onset mania.

Methods: Study participants were adults with unipolar major depression, scores of ≥17 on the Hamilton Rating Scale for Depression (HAM-D), and a low risk of suicide. They were randomly assigned to receive tDCS with a drug placebo, sham tDCS with escitalopram, or sham tDCS and placebo. tDCS was administered to the dorsolateral prefrontal cortex in 22 sessions (30 minutes each) over 10 weeks. Escitalopram was initiated at 10 mg/day for the first 3 weeks, and then increased to 20 mg/day. The primary study outcome was change from baseline to week 10 in HAM-D score.

Results: A total of 245 patients were randomized, and 202 completed all 22 sessions of real or sham tDCS. Mean HAM-D scores decreased from baseline in all 3 treatment groups.

(See table.) Although patients who received tDCS experienced significantly greater improvement than those who received placebo, the treatment did not meet the prespecified noninferiority threshold set at 50% of the difference between escitalopram and placebo. The difference between escitalopram and placebo in HAM-D change was 5.5 points, while the difference between tDCS and escitalopram was 2.3 points.

Outcomes after 10 weeks of treatment					
	Baseline HAM-D	10-Week HAM-D	Significance vs Placebo	Response	Remission
tDCS plus Placebo	21.8	12.8	p=0.01	39%	24%
Sham tDCS plus Escitalopram	21.7	10.4	p<0.001	47%	30%
Sham tDCS plus Placebo	22.7	16.9	—	22%	13%

Secondary analyses found both escitalopram and tDCS significantly superior to placebo among patients who had high adherence to treatment (p<0.001 and p=0.01, respectively), and the 2 active treatments did not differ from each other. Rates of response and remission, defined as a >50% decrease in HAM-D score and a final score of ≤7, respectively, not differ significantly between tDCS and escitalopram.

Compared with the other treatments, tDCS was associated with a higher incidence of local adverse events such as itching and irritation, as well as tinnitus and nervousness. Two patients in the tDCS group had new-onset mania, which did not result in study discontinuation or specific treatment. They were followed for an additional 6 months and did not have further manic or hypomanic symptoms. Escitalopram was associated with higher rates of sleepiness and severe constipation. No patient in any group was hospitalized or experienced suicidality.

Discussion: Although tDCS did not show noninferiority to escitalopram in this study, patients in each active treatment group showed similar improvement. The authors note that the sample size was small and results were based on continuous outcomes, thus the analyses may have been underpowered. In addition, patients who received escitalopram were able to guess their assigned therapy, presumably because of adverse effects, which may have inflated efficacy and invalidated the noninferiority comparison.[2]

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

[1]Brunoni A, Moffa A, Sampaio-Junior B, Borrione L, et al: Trial of electrical direct-current therapy versus escitalopram for depression. *NEJM* 2017;376 (June 29):2523–2533. From the University of Sao Paulo, Brazil. **Funded by the Fundacao de Amparo a Pesquisa do Estado de Sao Paulo; and other sources. Three of 17 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Lisanby S: Noninvasive brain stimulation for depression—the devil is in the dosing [editorial]. *NEJM* 2017;376 (June 29):2593–2594. From the NIMH, Bethesda, MD. **The authors disclosed financial relationships with commercial sources, including Brainsway, manufacturer of a brain stimulation device.**

***See Reference Guide.**

Sugar Intake and Mental Health

According to the results of a longitudinal study, intake of sugar from sweet foods and beverages adversely affects long-term mental health.

Background: Average sugar intake is twice the recommended level in Britain and 3 times higher than recommended in the U.S. Higher sugar consumption has been linked with depression in several ecological and cross-sectional studies, but the association has not previously been investigated longitudinally. Plausible biological explanations for the association include sugar-related

decreases in the production of brain-derived neurotrophic factor; increases in circulating inflammatory markers; hypoglycemia influencing mood states via altered hormone levels; addiction-like effects of sugar on dopamine neurotransmission; and obesity.

Methods: Investigators analyzed data from the Whitehall Study II, an ongoing study of a cohort of civil servants in London. Participants were recruited in 1985–1988, when they were aged 35–55 years, and were followed via 11 rounds of questionnaires, the most recent in 2012–2013. Diet was assessed using a food frequency questionnaire, based on the one used in the Nurses' Health Study, with 15 items comprising sweet food and beverages. Sugar intake was estimated using each food item's average sugar content and standard portion size. The General Health Questionnaire was used to assess nonpsychotic and minor psychiatric symptoms with the presence of ≥5 symptoms termed "common mental disorder" (CMD). In addition, the Center for Epidemiologic Studies Depression Scale (CES-D) was used to measure depression specifically.

Results: The cohort consisted of >8000 individuals (70% men) with >23,000 observations. Cross-sectional analysis showed that sugar intake was positively associated with CMD. In a model fully adjusted for demographic, health-related, and dietary factors, CMD was significantly more frequent in the highest tertile of sugar consumption, compared with the lowest tertile (odds ratio,* 1.17; p=0.011 for trend across all 3 tertiles). After accounting for age, gender, and ethnicity, high sugar intake was also associated with a higher prevalence of depression on the CES-D (odds ratio, 1.36; p=0.016), but the association was attenuated and no longer significant in the fully adjusted model. The prospective analysis was conducted separately by gender with inconsistent results. Sugar intake was not associated with any mental health outcome after 10 years. Over time, sugar intake decreased on average in the entire cohort. Neither CMD nor depression predicted 5-year change in sugar intake, contradicting the hypothesis of reverse causation.

Knüppel A, Shipley M, Llewellyn C, Brunner E: Sugar intake from sweet food and beverages, common mental disorder and depression: prospective findings from the Whitehall II study. *Scientific Reports* 2017; doi 10.1038/s41598-017-05649-7. From University College London, U.K. **Funded by the U.K. Medical Research Council; the NIH; and other sources. The authors declared no competing interests.**

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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.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

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). The rating checklists are posted at www.alertpubs.com.

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fMRI Neurofeedback for Major Depression

In a controlled trial, functional MRI neurofeedback training to increase the amygdala hemodynamic response to positive memories increased patients' recall of specific positive memories on an autobiographical memory test and decreased depression severity.

Methods: Study participants were unmedicated adults who met DSM-IV-TR criteria for major depressive disorder. The active study treatment consisted of real-time fMRI neurofeedback while patients recalled happy memories in an attempt to increase hemodynamic activity to the amygdala, which was represented by a bar showing the target activation level. The control group carried out the same task, with neurofeedback from a brain region uninvolved in emotion regulation. Participants completed 4 study visits, separated by 5–7 days. On all visits, they completed standardized assessments of depression and anxiety and the Autobiographical Memory Test, which consists of prompts to recall specific memories to match 18 words, 6 each with positive, neutral, and negative emotional valence. They underwent fMRI neurofeedback during the second and third visits. The primary study outcome was the difference between groups in change from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS). The Hamilton Rating Scale for Depression (HAM-D), the Beck Depression Inventory-II (BDI-II), and the Hamilton Rating Scale for Anxiety (HAM-A) were secondary outcome measures.

Results: Of 36 enrolled subjects, 2 withdrew because of discomfort during imaging and 1 could not be evaluated because of excessive head motion. Of the remaining 33 patients, three-fourths had chronic depression and more than half had previously received antidepressant medication.

Compared with the control group, all depression symptom ratings improved to a significantly greater extent between visits 1 and 4 in patients receiving active neurofeedback. Effect sizes* for active treatment were 1.17 on the MADRS, 0.92 on the HAM-D, and 0.74 on the BDI-II ($p \leq 0.03$ for all). Both treatment groups experienced comparable improvement in HAM-A scores.

Response criteria (≥50% decrease in MADRS score) were met by 12 of 18 participants in the experimental group and by 2 of 15 in the control group (67% vs 13%). Remission (MADRS

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score <10) was achieved by 6 and 2 patients, respectively (33% vs 13%). The number needed to treat* for response was 4.

Evaluation of hemodynamic activity showed a significant increase in amygdala activity only in patients receiving active treatment. The control group showed increased hemodynamic activity in their targeted brain region. The Autobiographical Memory Test also showed different patterns of response in the 2 groups. At visit 4, patients receiving amygdala feedback were able to recall more specific happy memories than controls ($p<0.004$). MADRS scores, amygdala activity, and positive specific memory recall at follow-up were statistically interrelated.

Discussion: Rates of remission with active treatment in this small sample were comparable to those generally seen with antidepressant medication and cognitive-behavioral therapy. However, the durability of response was not assessed. The modest placebo response in the study suggests that while recalling positive memories may have played some part in improvement, neurofeedback from the amygdala was crucial. Based on these results, neurofeedback appears to be a promising treatment for depression that is both safe and well tolerated and that may give patients a sense of control over their illness.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Young K, Siegle G, Zotev V, Phillips R, et al: Randomized clinical trial of real-time fMRI amygdala neurofeedback for major depressive disorder: effects on symptoms and autobiographical memory recall. *American Journal of Psychiatry* 2017;174 (August):748–755. From the Laureate Institute for Brain Research, Tulsa, OK; and other institutions. **Funded by the NIMH; and the National Alliance for Research on Schizophrenia and Depression. One study author disclosed a financial relationship with a study sponsor; the remaining 7 authors declared no competing interests.**

***See Reference Guide.**

Hospital Open-Door Policies and Aggression

Locked-door policies in psychiatric hospitals are based on the desire to protect patients from self-harm and the community from the actions of patients who have a high risk of aggressive behavior. However, a comparative study of hospitals with open- vs locked-door policies found little difference in patients' aggressive behavior.

Background: Aggression and violence have often been cited as justification for restrictive settings in inpatient psychiatric facilities. However, recent research suggests that a psychiatric diagnosis alone is not a sufficiently strong predictor of aggression or violence and that imposing restrictions on patients might actually aggravate violent behavior.

Methods: Study data were collected from 21 psychiatric hospitals serving a region of Germany. All institutions were located on general hospital sites: 16 had both open and locked ward types, 4 had only open wards, and 1 began using locked wards during the study period. The facilities are part of a single-tier mental health-care system, preventing selection of patients due to violent behavior or other potentially important clinical factors. Data were obtained from routine, standardized questionnaires, administered between 1998 and 2012. The primary study endpoint, aggressive behavior, was a composite of 3 types of behavior: aggressive behavior only, consisting of any interaction meant to inflict damage or unpleasantness on another person; bodily harm; and damage to property. Data compiled on the use of coercive measures, including seclusion and restraints, were also evaluated. Outcomes were compared using propensity score matching* based on numerous factors that would influence whether an individual was treated in a hospital with an open door policy, notably including prior aggressive behavior, and were analyzed on a hospital and specific ward level.

Results: The sample included >246,000 inpatients treated in a hospital with a closed-door policy and >68,000 treated in open-door hospitals. Propensity score matching resulted in 63,134 pairs of patients admitted to either type of hospital.

In the hospital-level analysis, the type of door policy (open vs locked) had no effect on the occurrence of any aggressive behavior or on any subtype of aggressive behavior. However, restraint and seclusion were significantly less likely to be used in hospitals with an open-door policy (odds ratio,* 0.369; p=0.002). In the ward-level analyses, open wards were associated with significantly less aggressive behavior and use of seclusion or restraints than locked wards. (See table.) The relationship was not consistent across types of aggression; while less restrictive wards were associated with less overall aggression, rates of bodily harm and property damage were higher in this setting.

Significant Differences in Aggressive Behavior, Seclusion, or Restraint Based on Ward Type

	Odds Ratio	Significance
Open Wards		
Any aggressive behavior	0.87	p=0.014
Aggressive behavior only	0.805	p<0.001
Bodily harm	1.451	p=0.007
Seclusion or restraint	0.647	p<0.001
Partially Locked Wards		
Damage to property	1.72	p=0.016
Bodily harm	1.879	p=0.001

Discussion: These results suggest that implementing a locked-door policy does not produce the intended reduction in aggression. On the contrary, open-door hospitals are associated with less use of coercive means to control patients, possibly leading to a better ward atmosphere. The secondary analysis by ward type suggests that it may be the open wards themselves that are beneficial in reducing aggression. In addition, open wards may reflect a therapeutic approach based more on building trust and less on control and coercion. The observations on partially locked wards appear contradictory and suggest that when staff has the option of locking doors, exercising that option might increase violent behavior. Results of this study are consistent with policies and treatment approaches that respect patients' autonomy and reduce institutional coercion.

Schneeberger A, Kowalinski E, Frohlich D, Schroeder K, et al: Aggression and violence in psychiatric hospitals with and without open door policies: a 15-year naturalistic observational study. *Journal of Psychiatric Research* 2017; doi:10.1016/jpsychires.2017.08.017. From the University of Basel, Switzerland; and other institutions. **This study was conducted without external funding. The authors declared no competing interests.**

***See Reference Guide.**

HIV and Hepatitis Risk in Severe Mental Illness

In a Swedish population study, the prevalence of blood-borne viral infections—HIV and hepatitis B (HBV) and C (HCV)—was elevated 2–8-fold in persons with severe mental illness. These infections may contribute to the reduced life expectancy of those with mental illness.

Methods: This cross-sectional analysis used data from Swedish registries of vital statistics and health care. Severe mental illness was defined as a clinical diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or other psychotic illness. Reporting of the 3 types of blood-borne viral infections is mandatory in Sweden and is linked to the national patient database. The analysis controlled for multiple potential risk factors: age, gender, ethnicity (Swedish

or immigrant), socioeconomic status, education, and substance misuse (based on a clinical diagnosis or a prescription for opiate replacement therapy).

Results: The total adult Swedish population was more than 6.8 million, of whom nearly 98,000 (1.43%) had a diagnosis of severe mental illness. The prevalence of each of the infections was elevated in persons with severe mental illness: unadjusted odds ratios* were 2.79 for HIV, 2.50 for HBV, and 8.63 for HCV. Odds ratios were attenuated after adjustment for potential risk factors, and in a model that included all except substance misuse, odds ratios ranged from 2.29 to 6.18. Odds ratios were further reduced, but remained statistically significant ($p<0.0001$) in the fully adjusted model that included substance misuse. (See table.) Risk for each infection was elevated for each of the mental health diagnoses analyzed separately.

Infection with a single blood-borne virus: fully adjusted model			
Infection	**Total Population (6.8 million)**	**Severe mental Illness (98,000)**	**Odds ratio**
HIV	5909 (0.09%)	230 (0.24%)	1.61
Hepatitis B	14,783 (0.22%)	518 (0.53%)	1.28
Hepatitis C	41,600 (0.61%)	4476 (4.58%)	1.72

Discussion: In addition to increasing mortality, blood-borne viral infections in the mentally ill increase stigma and disability and adversely affect quality of life and illness course. National guidelines for treating health problems in the mentally ill pay little attention to infectious disease and sexual health. Routine availability of testing for blood-borne infections during contacts with mental health and substance abuse services along with preventive strategies could reduce the risk of these infections. The most beneficial avenue to reduce infection rates may be harm reduction strategies for substance misuse, the strongest risk factor.

Bauer-Staeb C, Jorgensen L, Lewis G, Dalman C, et al: Prevalence and risk factors for HIV, hepatitis B, and hepatitis C in people with severe mental illness: a total population study of Sweden. *Lancet Psychiatry* 2017;4 (September):685–693. From University College London, U.K.; and the Karolinska Institute, Stockholm, Sweden. **Funded by the Medical Research Council; and Swedish Research Council. The authors declare no competing interests.**

***See Reference Guide.**

Single-Session Transcranial Stimulation for Bulimia

In a proof-of-concept study, a single session of transcranial direct current stimulation (tDCS) transiently improved symptoms of bulimia nervosa.

Background: Unhealthy eating behavior in bulimia nervosa may be triggered by disturbances in reward processing and self-regulatory control, both of which are associated with altered neurocircuitry in the dorsolateral prefrontal cortex (DLPFC). Preliminary studies have shown that repetitive transcranial magnetic stimulation (rTMS) of the DLPFC is promising in the treatment of bulimia. Potential advantages of tDCS over rTMS include its portability, cost, and favorable safety–feasibility profile, as well as the fact that it can be applied bilaterally.

Methods: Study participants were 37 women and 2 men, aged ≥18 years, who were recruited clinically or from advertising and were screened by telephone to confirm they met DSM-5 diagnostic criteria for bulimia nervosa. In randomized crossover fashion, participants received 2 sessions of bilateral tDCS over the DLPFC and a single sham session. The polarity of the electrodes was reversed between the 2 active treatment sessions: anode (excitatory) right/cathode (inhibitory) left or vice versa (AR/CL or AL/CR). All sessions lasted 20 minutes, with the sham treatment consisting of active current only for the first 30 seconds.

Sessions were separated by ≥2 days, and outcomes were measured over 24 hours. The primary outcome of interest was change from pre- to posttreatment in the urge to binge-eat, measured using a visual-analogue scale.

Results: Participants had a mean age of 26 years and a mean body mass index of 22. On average, they binged and vomited 8 times per week and, to a lesser extent, used laxatives and diuretics or excessive exercise. Most patients reported severe levels of depression (56%), anxiety (44%), and/or stress (36%).

Visual-analogue scores for the urge to binge-eat were reduced significantly after both types of active tDCS treatment (p=0.016 for AR/CL and p=0.012 for AL/CR, respectively), but not after sham tDCS. Mean global scores on the Mizes Eating Disorder Cognition Questionnaire-Revised decreased only after AR/CL treatment. However, during the 24 hours after treatment, all 3 interventions were associated with similar levels of binge eating, laxative or diuretic use, and excessive exercise. Changes in the wanting and liking of specific types of food (e.g., sweet foods, savory foods) also did not differ between treatments. Self-regulatory control was improved after both of the active treatment sessions, but not after sham treatment. Global scores on the Profile of Mood States assessment indicated a reduction in total mood disturbance, but the change was significant only with AR/CL tDCS. Changes in cortical excitability appeared to diminish approximately 1–2 hours post-stimulation.

Discussion: The benefits of tDCS in this study were modest and transient, but multiple sessions could produce long-lasting clinical gains. The polarity effect seen in this study is consistent with research suggesting that alterations in executive function may be lateralized in bulimia.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Kekic M, McClelland J, Bartholdy S, Boysen E, et al: Single-session direct current stimulation temporarily improves symptoms, mood, and self-regulatory control in bulimia nervosa: a randomised controlled trial. *PLOS One* 2017; doi 10.1371/journal.pone.0167606. From King's College London, U.K. **Funded by the U.K. Medical Research Council; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Residual Symptoms and Depression Relapse

Individual residual depressive symptoms may help identify patients with increased likelihood of relapse, according to a post-hoc analysis of data form the STAR*D trial. Clinician-rated and patient-rated symptoms appear to be equally valid predictors.

Methods: The STAR*D trial was an NIMH-funded study of stepped treatment for major depressive disorder. All participants received citalopram (*Celexa*) for 12–14 weeks as their first antidepressant medication. The present study included 1133 patients who achieved remission or a meaningful response during this phase and entered a 12-month naturalistic follow-up. The protocol recommended that patients continue with citalopram, but they could receive different medications or psychotherapies at their therapists' discretion. Beginning at the start of the follow-up period, 14 individual residual symptoms were assessed using the 16-item Quick Inventory for Depressive Symptomatology self-report (QIDS-SR-16) and the 16-item clinician-rated QIDS-C-16. Patients continued to report their symptoms using an automated telephone system every month. Relapse was defined as a QIDS-SR-16 score of ≥11.

Results: Of the >1100 patients, 454 (40%) experienced a relapse during the year of observation. All of the individual symptoms (see table, next page) contributed to relapse prediction. However, an adjusted survival analysis identified 3 self-report and 3 clinician-rated symptoms that remained statistically significant. Clinician-rated symptoms that were significantly

predictive of relapse were restlessness (hazard ratio [HR],*1.3; p=0.001) weight change (HR, 1.1; p<0.05), and sleep-onset insomnia (HR, 1.1; p<0.05). Self-reported predictive symptoms also included restlessness (HR, 1.2; p=0.01) and weight change (HR, 1.1; p=0.04) as well as hypersomnia (HR, 1.2; p=0.009). Scores that summed all 3 items had higher predictive accuracy than individual items.

Discussion: Previous research on relapse prediction based on residual symptoms has focused on summed scores of symptom scales. The few studies assessing individual symptoms have had small sample sizes. The present study indicates that abbreviated symptom scales focusing on specific symptoms may be relevant in real-world practice. However, caution is warranted because the STAR*D study population was highly selective and results may not generalize to all populations.

Prevalence of Individual Residual Symptoms		
Symptom	**QIDS-SR-16**	**QIDS-C-16**
Sleep onset insomnia	34.5%	29.6%
Mid-nocturnal insomnia	74.1%	58.2%
Early morning insomnia	18.2%	18.2%
Hypersomnia	28.8%	28.5%
Sad mood	40.5%	31.5%
Appetite change	32.0%	23.5%
Weight change	34.8%	32.0%
Impaired concentration/ decision-making	30.6%	31.8%
Negative self-view	15.6%	22.4%
Suicidal ideation	7.2%	5.9%
Lack of involvement	22.9%	22.6%
Loss of energy	28.9%	41.9%
Slowed down	10.5%	14.6%
Restlessness	26.9%	27.6%

Sakurai H, Suzuki T, Yoshimura K, Mimura M, et al: Predicting relapse with individual residual symptoms in major depressive disorder: a reanalysis of the STAR*D data. *Psychopharmacology* 2017;234:2453–2461. From Keio University **School of Medicine, Tokyo, Japan; and the Centre for Addiction and Mental Health, Toronto, Canada. The present analysis was conducted without funding; the STAR*D trial was funded by the NIMH. Four of 5 study authors disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

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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.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

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.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

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). The rating checklists are posted at www.alertpubs.com.

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Sleep Deprivation for Depression

Acute sleep deprivation produces rapid antidepressant responses in about half of patients, according to a meta-analysis. Effects were similar in patients with unipolar and bipolar depression and whether sleep deprivation was total (lasting 36 hours) or partial. The analysis did not reach any conclusions about ways to prolong the benefits of sleep deprivation, which are usually lost after a night's sleep.

Methods: The meta-analysis included English-language studies of experimentally induced sleep deprivation in patients with depression. Studies were included regardless of whether there was a control group, but were required to use a defined rating scale for response. Studies were excluded if they had <5 subjects, sleep deprivation was augmented with chronotherapeutics (e.g., phase advance or bright light therapy) or other interventions such as repetitive transcranial magnetic stimulation (rTMS), or the sample included subjects with other than pure or bipolar depression, such as seasonal affective disorder. Response in individual studies was defined a ≥30%, 40%, 50% reduction in standardized depression rating scale scores, or as non-percentage based reduction in symptoms.

Results: The analysis included 66 studies, conducted between 1976 and 2012, with a mean sample size of 23. Only 9 of the studies were randomized, which precluded subgroup analyses and assessment of publication bias for that group of studies.

Randomized studies included 141 participants who underwent sleep deprivation, of these, 63 participants (44.5%) were considered responders. Among nearly 1600 participants in non-randomized trials, 812 were considered responders (50.4%). Rates of response were similar for total and partial sleep deprivation. Multiple administrations of sleep deprivation were associated with a 38% overall response rate. The response rate was 51% in unipolar depression, 38% in bipolar depression, and 53% in mixed samples. Response rates were similar for all definitions and did not differ according to type of depression, medication status, age, gender, or type of sleep deprivation.

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Discussion: Studies included in the meta-analysis were highly heterogeneous, and the analysis excluded a large number of studies, conducted primarily in patients with bipolar disorder, that provided chronotherapeutics along with sleep deprivation. These studies reportedly had relatively high response rates of 45–79%. Some literature indicates that adding chronotherapeutics to sleep deprivation could help sustain clinical improvement.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Boland E, Rao H, Dinges D, Smith R, et al: Meta-analysis of the antidepressant effects of acute sleep deprivation. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16r11332. From Corporal Michael J. Crescenz VA Medical Center; and the University of Pennsylvania, Philadelphia. **Funded by the Department of Veterans Affairs; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Acceptance and Commitment Therapy for Substance Use Disorders

In a pilot study, acceptance and commitment therapy (ACT) was associated with improvement in psychological flexibility and executive function in patients institutionalized for severe substance use problems.

Methods: The study was conducted within a Swedish government agency that institutionalizes patients with substance use disorders for compulsory care. These patients are high-risk, typically with other mental health disorders that may trigger relapse, as well as problems such as brain trauma and ADHD. Participants were 18 patients with a severe drug or alcohol use disorder, living in 1 of the institutional homes. The investigators developed a manual for a course of ACT, delivered in 7 sessions (90-minutes each) over 3 weeks, based on the 6 key processes of the therapy and including brief daily mindfulness practices. The main objectives of ACT are to instill psychological flexibility, allowing the individual to avoid giving in to impulses, and to enhance executive function. Study outcomes were mental health status, measured with the 21-item Depression, Anxiety, and Stress Scale; psychological flexibility, measured using the Acceptance and Action Questionnaire-II; and executive function, evaluated with the Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A), which includes indices for behavioral regulation and metacognition.

Results: At study end, patients showed no overall change in mental health. However, psychological flexibility improved in 12 clients (67%), was unchanged in 4 (22%), and worsened in 2 (11%). Executive function also improved as evidenced by decreases in score on all 4 BRIEF-A subscales relating to behavioral regulation (i.e., inhibition, shift, emotional control, self-monitoring); effects were strongest on the inhibition domain. Among the 5 metacognition subscales (i.e., initiation, working memory, plan/organize, task monitoring, organization of materials), participants showed improvement in all except organization of materials. The greatest gains were seen for task monitoring. Overall, 31% of patients were generally improved in behavioral regulation and executive function, 57% were unchanged, and 12% worsened.

Discussion: Relatively short exposure to ACT was previously shown to have positive effects on outpatients with substance use disorders. Results of this study extend those findings to a larger patient population. However, the authors note that because patients tended to have multiple serious problems and the sample was too small to perform statistical tests, results may not be generalizable. Nevertheless, the results suggest ACT deserves further investigation in institutional settings.

Svanberg G, Munck I, Levander M: Acceptance and commitment therapy for clients institutionalized for severe substance-use disorder: a pilot study. *Substance Abuse and Rehabilitation* 2017;8:45–51. From the Swedish National Board of Institutional Care (SiS), Stockholm; and other institutions. **Funded by the SiS. The authors declared no competing interests.**

Compliance with Self-Harm Command Hallucinations

Patients with self-harm command hallucinations were more likely to comply with the hallucinations if they had a history of childhood abuse, a current substance use disorder, or belief about compliance in the future, according to results of a retrospective study.

Methods: Risk factors for compliance with self-harm command hallucinations were retrospectively evaluated in individuals with psychosis who were admitted to 1 of 3 acute inpatient facilities. Patients had a DSM-IV diagnosis of a psychotic disorder or an affective disorder with psychotic features, reported auditory command hallucinations in the previous 2 months, and reported choosing to comply or not comply with the command (i.e., suicidal behavior) in the week before hospitalization. Multiple standardized assessments including the Auditory Hallucinations Schedule, developed for this study, assessed auditory hallucination experiences, family history, and clinical status.

Results: The study population consisted of 28 men and 54 women, with either affective disorders (60%), schizophrenia spectrum disorders (35%), or borderline personality disorder (5%). A total of 32 patients complied with their command hallucinations and 50 resisted. The majority of patients (79%) reported a history of childhood physical abuse, which was frequent in nearly half of patients, and 19 patients had a comorbid substance use disorder.

Patients who complied with the command hallucinations were more likely to have a self-reported history of compliance with command hallucinations, believed that they had to obey the voice, and had a higher perception of compliance in the future. In a multivariate analysis, 3 factors were significantly associated with increased risk for compliance: severity of childhood physical abuse (odds ratio,* 5.41; p=0.001); belief about compliance in the future (odds ratio, 2.96; p=0.009); and current substance use disorders (odds ratio, 5.76; p=0.009). The multivariate model classified compliance and resistance with 84% accuracy.

Discussion: This study is limited by its cross-sectional nature, and there is a need for prospective studies of compliance with self-harm command hallucinations. The 3 risk factors identified had excellent classification accuracy, which suggests they may be useful in clinical risk assessment for suicidal behavior. They may also be suitable targets for intervention.

Dugré J, Guay J, Dumais A: Risk factors of compliance with self-harm command hallucinations in individuals with affective and non-affective psychosis. *Schizophrenia Research* 2017; doi 10.1016/j.schres.2017.09.001. From the Research Center of the Montreal Mental Health University Institute, Canada; and other institutions. **This research was conducted without funding. The authors declared no competing interests.**

***See Reference Guide.**

Maintenance rTMS for Treatment-Resistant Depression

Weekly repetitive transcranial magnetic stimulation may be helpful in maintaining antidepressant response in patients with treatment-resistant depression, according to a randomized, sham-controlled trial. However, the high dropout rate at 6 months suggests that prolonged maintenance rTMS may not benefit all patients.

Methods: The study provided 1 month of daily (Monday–Friday) rTMS in an open-label manner to patients with treatment-resistant unipolar or bipolar depression. Clinical response was defined as a ≥50% decrease in Hamilton Rating Scale for Depression (HAM-D) score. Patients who achieved response after the 20 sessions of acute treatment were randomly assigned to double-blind maintenance with real or sham rTMS. Maintenance treatment frequency was 3 sessions per week for 2 weeks, followed by 2 sessions per week for 2 weeks, then 1 session per week for 2 months, and finally 1 session every 2 weeks for 8 months. Active rTMS was delivered at 10 MHz over the left dorsolateral prefrontal cortex.

Results: Of 58 patients enrolled in the open-label phase, 35 met response criteria, including 16 who achieved remission (i.e., HAM-D score <8). Of these patients, 17 consented to randomized maintenance: 10 received active rTMS and 7 received sham treatment. All patients completed maintenance treatment through the second month with active rTMS and the fourth month with sham treatment. By 6 months, the nearly 30% dropout rate from the start of randomized treatment was too high to compare outcomes between the 2 groups statistically. Reasons for withdrawal included treatment response, remission, relapse, and relocation. A total of 3 patients in the active rTMS group and 2 in the sham group completed the 11 months of scheduled treatments.

Between months 1 and 4, patients who received active rTMS showed greater improvement in average HAM-D score than those receiving sham treatment, the between-group difference was not significant until the 4-month evaluation (p=0.03), and the statistical significance did not survive correction for multiple comparisons. However, between the 1- and 4-month assessments, HAM-D scores decreased in 5 of 9 patients who received active treatment and completed the 4-month assessment, remained at the same level in 3 patients, and worsened in 1. In contrast, scores worsened in 5 of 7 sham-treated patients and improved (by 1 point each) in 2 patients. Secondary endpoints, including other ratings of depression, anxiety, and overall illness severity, did not differ between the real and sham rTMS groups at any time.

Discussion: The absence of a significant between-group difference in the first months suggests that patients who received sham rTMS may have been experiencing carryover effects of acute treatment. One session per week appears to be enough to maintain the antidepressant response, but treatment every other week appears insufficient. Decreasing the frequency of maintenance rTMS more gradually than was done in the present study (e.g., 3 sessions per week for 1 month, then 2 sessions per week for 1 month) could have improved outcomes.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial; however, the authors did not disclose the source of funding.

Benadhira B, Thomas F, Bouaziz N, Braha S, et al: A randomized, sham-controlled study of maintenance rTMS for treatment-resistant depression (TRD). *Psychiatry Research* 2017; doi:10.1016/j.psychres.2017.08.029. From the Etablissement Public de Santé Ville-Evrard, Neuilly sur Marne, France. **Source of funding not stated. The authors declared no competing interests.**

***See Reference Guide.**

Suicide Patterns in Adults

Based on survey results from a representative sample of U.S. adults, suicide rates are increasing. The increase appears to disproportionately affect younger adults, those with less formal education, and those with a history of violence, prior suicide attempts, or common personality, mood, and anxiety disorders.

Methods: Data for the analysis was collected from 2 successive waves (2004–2005 and 2012–2013) of the National Epidemiologic Survey on Alcohol and Related Conditions, conducted by the National Institute on Alcohol Abuse and Alcoholism. Each cohort consisted of >34,000 respondents aged ≥21 years who completed a face-to-face questionnaire. A recent suicide attempt was defined as occurring in the past 3 years; earlier occurrences were defined as a history of suicide attempts.

Results: The 2 cohorts comprised 69,341 participants with a mean age of 48 years (57% women). The percentage of adults reporting a recent suicide attempt increased significantly from 0.62% in 2004–2005 to 0.79% in 2012–2013 (p=0.04). In the more recent survey, a prior suicide attempt was by far the strongest predictor of a recent attempt. (See table, next page.) Risk of a recent

attempt was higher in women; younger individuals; persons who were unmarried, divorced, or widowed; the unemployed; and those with less education or lower income. Suicide attempts were associated with a lifetime history of violent behavior.

Recent suicide attempt prevalence in selected groups+		
Characteristic	**Prevalence**	**Adjusted odds ratio***
Female	0.92%	1.52
Aged 21–34 years	1.48%	12.65
High school education	1.01%	4.05
Unemployed	1.15%	3.37
Annual family income <$20,000	1.67%	5.71
Past-year borderline personality	4.57%	13.55
Lifetime violent behavior	2.74%	6.64
Prior suicide attempt	9.17%	23.54

+The prevalence of recent suicide attempt is contrasted between the reference group, with the lowest rate for each characteristic, and the group with the highest prevalence

Strikingly, in both survey waves, nearly two-thirds of adults with a recent suicide attempt had borderline personality disorder, a group with a nearly 14-fold increase in the odds of suicide compared with those without a mental disorder. Odds ratios for other psychiatric disorders within the year before suicide attempt, including depression, anxiety, substance use, antisocial personality, and schizoptypal personality, ranged from 4.52 to 8.51, relative to persons without a disorder.

Discussion: The patterns of suicide attempts uncovered in the study indicate that suicide prevention programs should be focused on younger, economically disadvantaged adults, particularly those with personality, mood, or anxiety disorders or with a history of violence or suicide attempt.

Olfson M, Blanco C, Wall M, Liu S-M, et al: National trends in suicide attempts among adults in the United States. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.2582. From the College of Physicians and Surgeons, Columbia University, New York; and other institutions. **Funded by the NIH; and the New York State Psychiatric Institute. The authors declared no competing interests.**

***See Reference Guide.**

Anxiety Prevention

Programs to prevent anxiety disorders or reduce anxiety symptoms in the general population have small but significant effects, according to a systematic review and meta-analysis.[1]

Methods: The analysis included all identifiable randomized controlled trials (RCTs) of educational or psychological interventions for anxiety. Educational interventions included lectures or fact sheets, and psychological interventions attempted to change how people think using specific strategies such as a cognitive-behavioral approach. Allowed comparators were care-as-usual, no intervention, a waiting list, or attention control. Baseline anxiety was required to be measured in a standardized way, and studies were excluded if they provided the intervention to persons with an anxiety disorder diagnosis. Study outcomes were the incidence of new cases of any DSM-IV anxiety disorder and/or reduction of scores on a standardized measure of anxiety symptoms. Posttraumatic stress disorder was not considered because it is difficult to separate prevention of this disorder from treatment.

Results: The literature search identified 29 randomized trials with a total of 10,430 patients. Most interventions (n=25) were CBT-based, and the number of sessions ranged from 1 to 12. Follow-up periods ranged from 7 weeks to 60 months, with a median of 12 months. Prevention was indicated, selective, and universal in 11, 10, and 8 RCTs, respectively. Reduction in anxiety symptoms and incidence of anxiety disorder diagnosis were the primary outcome in 10 studies each; 9 studies evaluated both outcomes.

According to the meta-analysis, prevention programs were associated with reduced incidence of an anxiety disorder (pooled odds ratio,* 0.57; p<0.001), with considerable heterogeneity among studies. Programs were also associated with reduced anxiety symptoms (standardized mean difference,* -0.31; p<0.001). The treatment effects, although small, were robust despite evidence of publication bias and considerable heterogeneity among study results. Studies with a larger sample size and those with a low risk of bias tended to report smaller effects. Selective prevention interventions tended to be more effective than other types.

Discussion: Little information is available on cost effectiveness, but an accompanying editorial suggests that low-cost, brief psychoeducation programs may result in a significant decline in new cases of anxiety.[2] In addition, there does not appear to be a critical developmentally sensitive period for prevention; programs conducted in children or adults were equally effective.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

[1]Moreno-Peral P, Conejo-Cerón S, Rubio-Valera M, Fernandez A, et al: Effectiveness of psychological and/or educational interventions in the prevention of anxiety: a systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.2509. From the Research Unit, Primary Care District of Málaga - Guadalhorce, Málaga, Spain; and other institutions. **Funded by the Spanish Ministry of Health; and other sources. The authors declared no competing interests.**

[2]Hudson J: Prevention of anxiety disorders across the lifespan [editorial]. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.2430. From Macquarie University, Sydney, Australia. **The author disclosed a potentially relevant financial relationship.**

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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.

Standardized Mean Difference: The difference between 2 normalized means—i.e., the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

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). The rating checklists are posted at www.alertpubs.com.

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Digital Therapeutic App for Substance Use

The FDA has cleared the reSET® mobile application—the first prescription mobile medical app for the treatment of substance abuse—for marketing in the U.S. reSET delivers cognitive behavioral therapy designed to increase abstinence and foster retention in outpatient substance use treatment. It is intended to be used in conjunction with outpatient therapy in patients with addictions to alcohol, cocaine, marijuana, and/or stimulants; it is not intended to treat opioid dependence. When available, the mobile app will be marketed by Pear Therapeutics.

FDA News Release: FDA permits marketing of mobile medical application for substance use disorder. Available at https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm576087.htm.

Wearable Technology for Schizophrenia Monitoring

Reduced heart-rate variability is an indicator of autonomic dysregulation, which may be associated with functional difficulties and symptoms of schizophrenia. In a cross-sectional study, a watch-like mHealth (mobile health) device used to track physical activity and heart-rate variability in patients with schizophrenia was acceptable to patients and provided useful data on autonomic system functioning.

Background: Some research indicates autonomic dysregulation may be implicated in functional problems associated with schizophrenia. Reduced vagal tone and heart-rate variability have been linked with poorer function, illness chronicity, and positive and negative symptoms.

Methods: Study subjects were 30 adults with schizophrenia and a control group consisting of 25 age- and gender-matched volunteers from the community. Autonomic activation was measured with a wearable device equipped with 3 sensors that measured skin conductivity (a marker of sympathetic nervous system arousal), blood volume pulse (providing data to estimate heart-rate variability and related parameters), and acceleration (activity). After an initial evaluation, participants were briefed on the use of the device and instructed to wear it for 6 days, from waking until bedtime, removing it only to avoid getting it wet. Data were stored on the device

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until the participant returned it to the study clinic. Assessments in the clinic included the Positive and Negative Syndrome Scale for the patients with schizophrenia and questionnaires on time use (i.e., structured activity) and acceptability of the device for all of the study participants.

Results: At baseline, patients with schizophrenia reported that they spent a mean of 36 hours per week in structured activity, such as work, socializing, travel, chores, and child care. In contrast, controls spent an average of 108 hours in structured activity. All patients and controls were able to wear the device according to instructions. Acceptability was similar in patients and controls, with about 80% "good" or "excellent" acceptability ratings.

Compared with controls, patients with schizophrenia had significantly lower levels of heart-rate variability, indicating reduced parasympathetic activity, as well as lower levels of movement and functioning. In these patients, reduced parasympathetic activity was associated with positive symptom severity, and movement was correlated with negative symptoms. The number of self-reported weekly hours of structured activity correlated with measured movement levels. Medication was not associated with any of the autonomic parameters measured.

Discussion: It has been suggested that patients with schizophrenia may experience normal sympathetic reactions to arousing stimuli, but diminished parasympathetic activity prevents downregulation of this sympathetic arousal. Wearable mHealth devices such as the Empatica E4 used in the study provide a way to measure these phenomena outside the laboratory and also may be used to monitor disease fluctuations and support interventions to improve cardiometabolic health.

Cella M, Okruszek L, Lawrence M, Zarlenga V, et al: Using wearable technology to detect the autonomic signature of illness severity in schizophrenia. *Schizophrenia Research* 2017; doi 10.1016/j.schres.2017.09.028. From King's College London, U.K.; and the Polish Academy of Sciences, Warsaw. **This research was conducted without funding. The authors declared no competing interests.**

***See Reference Guide.**

Nerve Stimulator for Opioid Withdrawal

An electro auricular stimulation device, previously used in acupuncture, has now received FDA approval for the treatment of acute opioid withdrawal symptoms, which can include sweating, gastrointestinal upset, agitation, insomnia, and joint pain. The NSS-2 Bridge electric stimulator is a small, battery-powered device worn behind the ear that stimulates branches of certain cranial nerves and provides relief from opioid withdrawal symptoms. The device can be used for up to 5 days during acute physical withdrawal. NSS-2 Bridge is contraindicated in patients with hemophilia or psoriasis vulgaris and in patients with cardiac pacemakers.

In the clinical study upon which the approval was based, all 73 patients undergoing physical opioid withdrawal experienced a >30% reduction in withdrawal symptoms within 30 minutes of using the device and nearly all (88%) were able to transition to medication-assisted therapy after 5 days of device use.

FDA News Release: FDA grants marketing authorization of the first device for use in helping to reduce the symptoms of opioid withdrawal. Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585271.htm.

Invasive Neurostimulation Therapies

Electrical stimulation technologies are emerging from a decades-long static period, with new devices and imaging technologies offering the potential for more precise, individualized stimulation and closed-loop systems, according to a review. The invasive technologies have their greatest use in neurologic disorders, such as epilepsy and chronic pain, but their use in psychiatric disorders also continues to be explored.

Invasive neurostimulation therapies—i.e., deep brain stimulation (DBS), motor cortex stimulation (MCS), responsive neurostimulation (RNS), spinal cord stimulation (SCS), and vagus nerve stimulation (VNS)—are recognized as effective treatment for a growing number of medically resistant neurologic and neuropsychiatric disorders. These systems all consist of 3 implantable components: stimulating electrodes, an internalized pulse generator/battery pack, and subcutaneous electrode extenders connecting these 2 components. The surgical placement of the components depends in part on the anatomic location of the targeted dysfunctional circuitry and the patient's medical history. MCS, RNS, and SCS are primarily indicated for pain disorders and/or treatment of epilepsy, while DBS and VNS are often used to treat obsessive-compulsive disorder and resistant depression, respectively. In addition, DBS is currently being investigated for therapeutic potential in Tourette syndrome, resistant depression, addiction, and Alzheimer's disease.

Therapeutic mechanisms underlying the use of invasive brain stimulation are poorly understood. Nevertheless, invasive stimulation is expanding to new clinical applications. Technologies resulting from the 2013 Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative are expected to accelerate the move to personalized, long-term systems to treat many disorders. Traditional open-loop systems rely on clinician programming of the stimulation parameters. Newer, investigational closed-loop systems provide therapeutic stimulation upon detection of precursor signals to maximize therapeutic effects and minimize adverse effects.

High-resolution stimulating leads now provide more precise targeting of stimulation. Innovative structural and functional imaging technologies are improving the understanding of brain circuitry; for example, diffusion tensor imaging provides data about the white matter tracts that connect brain regions. Brain connectivity maps, called connectomes, are being linked with specific disorders, leading to greater understanding of how brain stimulation works and to individualized precise neuromodulation. Frameless stereotactic imaging devices allow for more rapid, precise electrode placement. Intraoperative electrocorticography sensorimotor cortex readings are identifying biomarkers for dysfunctional motor circuitry in patients with movement disorders. Other imaging advances include intraoperative readings to identify potential feedback mechanisms and in-vivo neurochemical monitoring, based on the activity of electroactive neurotransmitters such as dopamine and serotonin.

Advances in neurostimulation technology are occurring at a rapid pace and could lead to precise and adaptable neuromodulation therapies. However, there is need for a better understanding of the therapeutic mechanisms of neurostimulation as well as development of electrodes that provide long-term, highly precise assessment of feedback signals in real time.

Edwards C, Kouzani A, Lee K, Ross E: Neurostimulation devices for the treatment of neurologic disorders. *Mayo Clinic Proceedings* 2017;92 (September):1427–1444. From Deakin University, Geelong, Australia; and the Mayo Clinic, Rochester, MN. Source of funding not stated. **The authors did not include disclosure of potentially competing interests.**

Bone Marrow Transplant and Schizophrenia Remission

A patient with treatment-resistant schizophrenia experienced remission following a bone marrow transplant for cancer. At the most recent follow-up, 8 years after the transplant, the patient's remission persisted.

The patient presented at age 23 years with onset of insomnia, irritability, and anxiety, which progressed to agitation, persecutory delusions, and paranoid ideation. He received a diagnosis of DSM-IV-TR paranoid schizophrenia. Symptoms worsened after quetiapine was initiated. Risperidone and olanzapine were added without improvement in psychotic symptoms or social functioning. At age 24, the patient was found to have acute myeloid leukemia, for which a bone marrow transplant was recommended. Prior to the procedure, psychotropics

were discontinued and the patient was required to undergo a 7-day test isolation to determine whether he could handle the psychological pressure. After successfully completing the test, the patient underwent the bone marrow transplant and was isolated in a germ-free unit for 34 days. During this period, he received immunosuppressive therapy with cyclosporine and methotrexate. Tacrolimus was used later to treat early symptoms of graft-versus-host disease. The patient refused antipsychotic medication during the post-procedure isolation and following discharge. His psychotic symptoms were stable during isolation and had almost completely resolved by 30 days after discharge, as confirmed with a Positive and Negative Syndrome Scale score of about 30. Symptoms remained absent during 8 years of subsequent observation. The patient's social function, measured with the Global Assessment of Function Scale of DSM-IV-TR, also showed marked and stable improvement.

Discussion: Accumulating evidence suggests that neuroinflammation and immune system activation are involved in the pathophysiology of schizophrenia. Studies in animal models indicate bone marrow transplant can improve neurological disorders, possibly by normalizing malfunctioning microglia in the brain. While the procedure is not likely to be a cure for schizophrenia in all patients, the present report adds to the evidence supporting immunological pathogenesis of schizophrenia.

Miyaoka T, Wake R, Hashioka S, Hayashida M, et al: Remission of psychosis in treatment-resistant schizophrenia following bone marrow transplantation: a case report. *Frontiers in Psychiatry* 2017; doi 10.3389/fpsyt.2017.00174. From Shimane University School of Medicine, Japan. **The authors declared no competing interests.**

Common Drug Trade Names*: cyclosporine—*Sandimmune*; methotrexate—*Rheumatrex*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal*; tacrolimus—*Prograf

Adjunctive Bright Light Therapy for Bipolar Depression

Midday bright light therapy was effective as an adjunctive treatment for bipolar depression in a randomized trial.[1]

Background: In a previous pilot study in 4 patients with bipolar depression, these researchers found that morning bright light therapy was associated full response in 1 patient but emergence of hypomania in the remaining 3 patients.[2] Other investigators have shown that morning exposure is not effective in bipolar depression.[3]

Methods: The present study enrolled adults with bipolar I or II disorder, a current moderate or severe episode of depression, and no hypomania or mixed symptoms. Patients who had experienced a manic or hypomanic episode in the past 6 months were excluded. All participants received antimanic medication for ≥4 weeks, and pre-study antidepressants were prescribed as needed and remained unchanged during the study period. Patients were randomly assigned to receive double-blind treatment with either an active light box (7000-lux broad-spectrum white fluorescent) or an inactive unit (50-lux red light unit, chosen in part because it has been observed to reverse hypomania induced by morning bright light without affecting circadian rhythms). Treatment began with 15 minutes of light exposure between noon and 2:30 PM, increasing every week in 15-minute increments to 1 hour at week 4. The study had 2 primary efficacy outcomes: remission, defined as a Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS) score of ≤8 in weeks 4–6, and normal SIGH-ADS scores at the final visit.

Results: A total of 46 patients received treatment and were included in the efficacy analysis; 40 completed the study as planned. Patients had an average age of 45 years, had a mean age at onset of 16 years, and an average illness duration of nearly 29 years. Two-thirds of patients had a diagnosis of bipolar I disorder, and depression was generally moderate at the start of treatment. Ten patients were enrolled in February or March, when improvement in seasonal

depression might be expected. Nearly 80% of all study patients were taking an antidepressant, and all were taking a mood stabilizer.

Remission occurred in 15 patients receiving bright light, compared with 4 controls (68% vs 22%; adjusted odds ratio,* 12.64; p=0.004). The mean SIGH-ADS depression score at the last visit was 9.2 in patients who received active light therapy and 14.9 in controls (p=0.023). No patient experienced hypomania or a mood polarity switch. Secondary outcome measures indicated active light therapy was associated with greater improvement in global functioning, less anxiety, fewer social problems, fewer neurovegetative symptoms, and better sleep quality. Patients in both groups rarely experienced worsening of depression or emerging suicidal thoughts.

Discussion: The results of this study suggest that in patients with bipolar disorder, afternoon bright light therapy may be an effective option for patients with moderate-to-severe depression despite mood stabilizing therapy. The efficacy of afternoon, but not morning, light therapy in bipolar disorder suggests that the therapy may work via a different mechanism than the phase-resetting that occurs with morning light therapy in seasonal depression. The midday timing of treatment, gradual dose titration, and requirement for current antimanic treatment may have prevented the emergence of mania or hypomania in study participants.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

[1]Sit D, McGowan J, Wiltrout C, Diler R, et al: Adjunctive bright light therapy for bipolar depression: a randomized double-blind placebo-controlled trial. *American Journal of Psychiatry* 2017; doi: 10.1176/appi.ajp.2017.16101200. From Northwestern University, Chicago, IL; and other institutions. **Funded by the NIH; and other sources. The authors declared no competing interests.**

[2]Sit D, et al: Light therapy for bipolar disorder: a case series in women. *Bipolar Disorders* 2007;9:918–927.

[3]Dauphinais D, et al: Controlled trial of safety and efficacy of bright light therapy vs negative air ions in patients with bipolar depression. *Psychiatry Research* 2012;196:57–61.

***See Reference Guide.**

Long-Term Effects of Bibliotherapy in Depression

According to a systematic review, bibliotherapy is a useful self-help intervention that can produce long-term benefit in adults with depression.

Background: Bibliotherapy is a brief, non-pharmacological intervention that applies either cognitive or behavioral therapy techniques via the reading of a standard manual to teach patients strategies to control negative emotions as well as how to practice the techniques in everyday life. Research has shown bibliotherapy to be effective in patients with mild-to-moderate depression, but the long-term effects have not been established.

Methods: A comprehensive literature search was undertaken to identify randomized trials of bibliotherapy (or "reading therapy") for depression, published since 1990, with ≥3 months of follow-up. The primary outcome of interest was improvement in depression measured with a standardized scale, primarily the Hamilton Rating Scale for Depression or the Beck Depression Inventory.

Results: A total of 10 reports were identified: 6 conducted in the general adult population and 4 conducted in high school and/or college settings in adolescents or young adults with mild or subthreshold depression. Follow-up intervals ranged from 3 months in 4 studies to 3 years in 1 study. Most of the adult studies utilized a self-help book called *Feeling Good*, which is based on cognitive therapy principles, with delayed treatment offered as the control. One study used an additional self-help book, called *Control Your Depression*, which is based on behavioral principles. The young-adult studies generally offered cognitive self-help bibliotherapy as 1

of several randomized treatments that also included group cognitive behavioral therapy (CBT), journaling, supportive-expressive group therapy, and education.

In the 6 reports that documented depression change in nearly 400 adults, bibliotherapy—whether cognitive- or behavior-based, CBT, or interpersonal psychotherapy—significantly reduced depression rating scores. Improvements were maintained in all studies at the last follow-up visit. The 2 bibliotherapy approaches had similar efficacy. The 4 reports that described outcomes in about 1000 adolescents or young adults with subthreshold depression generally did not demonstrate long-term benefit of bibliotherapy.

Discussion: Bibliotherapy may have many advantages in treating depression on a population level: It is inexpensive and less time-consuming than conventional psychotherapy, is not stigmatizing, can provide immediate treatment, and is based on an efficient, high-quality therapeutic method that provides a structured approach for users to follow. The present analysis suggests that results are durable, but potentially only in adult populations.

Gualano M, Bert F, Martorana M, Voglino G, et al: The long-term effects of bibliotherapy in depression treatment: systematic review of randomized clinical trials. *Clinical Psychology Review* 2017; doi 10.1016/j.cpr.2017.09.006. From the University of Torino, Italy; and the Universita del Piemonte Orientale, Italy. **Source of funding not stated. The authors did not include disclosure of potentially competing interests.**

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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). The rating checklists are posted at www.alertpubs.com.

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Guided Self-Help CBT for Distressing Voices

A therapist-guided self-help cognitive behavioral therapy program had promising effects in reducing distress from hearing voices in a pilot study.[1] The randomized trial found the program was feasible and acceptable in a transdiagnostic group of patients.

Methods: The self-help CBT program was compared with a wait-listed control condition in patients currently receiving mental health care in the British National Health system. Participants were aged ≥18 years old, were distressed by hearing voices, and had a ≥12-month history of hearing the voices. Distress was quantified using 3 items from the Hamilton Program for Schizophrenic Voices Questionnaire (HPSVQ), measuring interference, distress from the voices, and negative effects on self-esteem. Other than substance misuse and organic illness, there were no diagnostic exclusions. Active treatment consisted of up to 8 therapist-guided sessions (1 hour each) using a published self-help book written by study authors[2] and an accompanying workbook developed for the study. The intervention consisted of modules addressing coping with voices, targeting negative beliefs about the self and unhelpful beliefs about voices, improving assertiveness in difficult relationships, and continuing use of new skills. The primary outcome was the 4-item voice impact subscale of the HPSVQ, administered at week 12.

Results: A total of 28 patients were enrolled: 13 with a psychosis spectrum diagnosis, 8 with borderline personality disorder, 4 with a mood disorder, 3 with another diagnosis. All but 2 were taking psychotropic medication, and 21 were taking at least 1 antipsychotic. Of the 14 patients randomized to active treatment, 2 did not begin treatment, 1 attended 4 sessions (the study-defined minimum exposure), and the rest attended 7 or 8 sessions. All but 1 patient who received active treatment reported that they were "very satisfied" with the program and their therapist. All 12 said that they would recommend the program to another person hearing distressing voices.

Treatment effects on actual voice characteristics such as frequency, duration, and volume, were small, compared with the waitlist control. However, the guided self-help CBT intervention was

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associated with large, significant reductions in voice impact (effect size,* 1.78). Secondary outcomes, including measures of anxiety, well-being, and patient-defined recovery, also favored the active intervention. Effects on depression were negligible. Outcome measures that addressed the program's mechanism of action found significant improvement in negative beliefs about the self, beliefs about voice omnipotence, and self-esteem, with effect sizes ranging from 0.83 to 1.13.

Discussion: The U.K. National Institute for Health and Care Excellence (NICE) guidelines recommend CBT for all patients with psychosis. However, few patients receive the treatment primarily because of a lack of access to therapists. Although preliminary, the present study results suggest that a self-guided CBT intervention, which could improve access to treatment, is both effective and acceptable to patients. Additional research is warranted.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

[1]Hazell C, Hayward M, Cavanagh K, Jones A, et al: Guided self-help cognitive-behaviour intervention for VoicEs (GiVE): results from a pilot randomised controlled trial in a transdiagnostic sample. *Schizophrenia Research* 2017; doi 10.1016/j.schres.2017.10.004. From the University of Sussex, Brighton; and the Sussex Education Centre, Hove, U.K. **Funded by the Economic and Social Research Council; and the Sussex Partnership NHS Foundation Trust. Two of 5 study authors disclosed relevant financial relationships; the remaining authors declared no competing interests.**

[2] Hayward M, et al: Overcoming Distressing Voices. London: Constable & Robinsons, Ltd., 2012.

***See Reference Guide.**

Avatar Therapy for Auditory Hallucinations

In a randomized controlled trial of patients experiencing auditory hallucinations, participation in Avatar therapy—a brief, manualized therapy based on dialogue with a digital representation of the voice—effectively changed the relationship of patients to their hallucinated voices. AVATAR therapy was also significantly superior to a control treatment after 12 weeks at reducing the severity of hallucinations, but the difference between treatments narrowed after an additional 12 weeks of follow-up.

Methods: Study subjects (n=150) were adults with a schizophrenia spectrum disorder or an affective disorder with psychotic symptoms who had been experiencing auditory hallucinations for ≥1 year. Participants were hearing an average of 3–4 voices at baseline and were asked to choose the voice they most wanted to influence. At entry, all patients were receiving antipsychotic medications that remained unchanged through the study period. Participants were randomized to receive either Avatar therapy or a control intervention in single-blind fashion. In Avatar therapy, patients first created a computerized representation of their most troublesome voice. Treatment was delivered in 6 subsequent weekly sessions, lasting 50 minutes each, by a therapist using a computer in a different room. Therapists could see and hear the patient on video and had the ability to switch between speaking with their own voice and as the avatar. All sessions were recorded as audio files and given to the patient to listen to at home. In the first 3 sessions, the avatar's speech was unchanged but the therapist encouraged the patient to respond assertively. In the remaining sessions, the avatar yielded ground and acknowledged the strengths and good qualities of the patient. The control treatment, also manualized, was a face-to-face supportive counseling approach in a non-directive way, using the same number and duration of sessions as Avatar therapy. The primary study outcome measure, assessed by blinded raters, was the total score on the Psychotic Symptom Rating Scales, auditory hallucinations subscale (PSYRATS–AH).

Results: A total of 20 randomized patients did not begin treatment, and 103 completed all sessions. The most common diagnosis was paranoid schizophrenia, the average illness duration was 20 years, and more than one-third of patients were prescribed clozapine (*Clozaril*). No

patient in either group was withdrawn by their referring therapist or study therapist because of adverse effects.

Compared with supportive counseling, Avatar therapy was associated with a significantly larger reduction in mean PSYRATS–AH total scores at week 12 (see table), as well as significantly lower scores on the subscales measuring frequency and distress. Ratings of malevolence or benevolence of the voices did not differ between the groups. At 12 weeks, Avatar therapy was associated with greater improvement in perceived omnipotence of the voices, measured using several scales. At week 12, 7 patients in the Avatar group and 2 in the control group reported hearing no voices in the previous week. By week 24, there was no longer any statistical difference between the groups, due to continued improvement in the supportive counseling group, and 8 and 6 patients in the Avatar and control groups, respectively, reported no hallucinations.

Results of AVATAR therapy versus supportive counseling

	Avatar Therapy	Supportive Counseling
PSYRATS–AH (possible range, 0–44)		
Baseline	29.6	30.5
week 12	22.8	27.5
week 24	22.2	25.2
PSYRATS–AH frequency (possible range, 0–12)		
Baseline	7.0	7.3
Week 12	5.2	6.7
Week 24	5.2	6.3
PSYRATS–AH distress (possible range, 0–20)		
Baseline	15.2	15.8
Week 12	11.1	13.8
Week 24	10.4	12.7

Discussion: The results of this trial support the rapid efficacy, feasibility, and acceptability of Avatar therapy for patients with auditory hallucinations. However, as this is the first randomized controlled trial of the intervention, there are several notable limitations including the absence of a treatment-as-usual control condition and the limited sample, which the researchers anticipate addressing in future trials.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Craig T, Rus-Calafell M, Ward T, Leff J, et al: AVATAR therapy for auditory verbal hallucinations in people with psychosis: a single-blind, randomised controlled trial. *Lancet Psychiatry* 2017; doi 10.1016/S2215–0366(17)30427–3. From King's College London, U.K; and other institutions. **Funded by the Wellcome Trust. Two of 8 study authors disclosed patents pending for the avatar system; the remaining authors declared no competing interests.** See related story in *Psychiatry Alerts NOS* 2014;6 (July):39.

***See Reference Guide.**

Cognitive Remediation in Bipolar Disorder

In a preliminary controlled trial, computer-based cognitive remediation produced lasting improvement in cognitive function in patients with bipolar I disorder and a history of psychosis.

Methods: Study participants were adult outpatients with stable bipolar I disorder. The study was limited to those with a history of psychosis to reduce study population heterogeneity and because psychosis is associated with more severe cognitive impairment. The active treatment—the BrainWorks program by Posit Science—was based on a recovery model of neural plasticity and consisted of sensory processing training during the early weeks, later adding work on higher-order functions. Difficulty of the tasks was adjusted to keep patients functioning at 80% proficiency. The control group participated in a nonspecific, unstructured program of computer games, with a similar format, number of training sessions, and amount of administrator contact. Both treatments involved 3 sessions per week—1 at the study site and 2 at the patient's location—with a target of 70 sessions. The clinic visits included a brief discussion linking program skills to daily life, for the active treatment arm only. The primary efficacy outcome was cognitive function, assessed by blinded raters with the MATRICS

Consensus Cognitive Battery (MCCB) at baseline, treatment midpoint, posttreatment, and after 6 months of no study contact.

Results: A total of 72 patients were enrolled and began treatment. The 2 groups completed a similar average number of sessions—43 for cognitive remediation and 48 for controls—and most gave their program moderate-to-high ratings for satisfaction. Of the total population, 17 patients discontinued treatment prematurely because of dissatisfaction with the time commitment; others were lost to follow-up or withdrew because of symptom exacerbations or because they were dissatisfied with the activities. About half of the participants in each group believed that they had been assigned to the active treatment.

With all enrolled participants included in the analysis, those who received the active intervention experienced greater overall improvement than controls in the MCCB cognitive battery composite score posttreatment (effect size,* 0.80; $p<0.05$) and 6 months later (effect size, 0.83; $p<0.05$). They also had a significantly larger mean improvement in visual learning posttreatment (effect size, 0.92; $p<0.05$) but not at follow-up; and larger mean improvement in processing speed at 6-month follow-up only (effect size, 0.65; $p<0.05$). Those who received active treatment also showed trend-level improvements either posttreatment or at 6 months in attention, working memory, verbal learning, and problem solving (effect sizes, 0.23–0.67). The control group also experienced posttreatment improvement in multiple cognitive domains, but the effect was lost at the 6-month follow-up. Both treatments had equivalent effects on domains of community functioning, suggesting that cognitive improvement did not translate to gains in this outcome. Improvements in cognitive function were not associated with changes in clinical symptom measures.

Discussion: The high rate of treatment dropout and the non-representativeness of the study sample, who had higher levels of pretreatment cognitive function than is typical of this patient population, limit the interpretation of these findings. However, the positive effects coupled with the cost effectiveness of a web-based treatment support additional research.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Lewandowski K, Sperry S, Cohen B, Norris L, et al: Treatment to enhance cognition in bipolar disorder (TREC-BD): efficacy of a randomized controlled trial of cognitive remediation versus active control. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.17m11476. From McLean Hospital, Belmont, MA; and other institutions. **Funded by the NIMH. Two of 7 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Male Attitudes Toward Depression

According to the results of a qualitative study, men with depression often do not seek help because of cultural and personal beliefs that depression and help-seeking are inconsistent with "masculine values."

Methods: The study was designed to explore reasons for the low rates of help-seeking in men with depression using Q methodology, an approach that identifies patterns of association among people's views. The investigators first identified an exhaustive list of statements about depression—both facts and opinions—from such sources as journal articles, conventional mass media, social media, and conversations. The search resulted in a "Q set" of 57 statements. Study participants were men, aged ≥18 years, with current depression, recruited from a psychological therapy service or the community. Participants were asked to sort the 57 statements according to how much they agreed with each one, relative to the others. They also completed a post-sort interview to comment on their choices. The Q sorts were analyzed to identify factors that explained the maximum amount of variance.

Results: Of 50 men who were screened and determined to be eligible, 15 did not schedule an appointment for the sort, 5 others did not attend, and 1 was too distressed by his depression to complete the sort. The analysis was based on 29 men, most with at least moderately severe depression.

The analysis identified 2 prevalent factors, each representing a different viewpoint. A total of 14 men acknowledged that help for depression was effective and available. However, they believed it was more "masculine" to cope with depression alone and that other men would judge them negatively for seeking help. This group felt that treatment made it worthwhile to overcome these barriers and help-seeking was viewed as courageous and activist, a duty to one's self and others. Men who endorsed this viewpoint generally had previous treatment with a positive result.

According to the second viewpoint, endorsed by 6 men, experiencing depression was blameworthy and failure to deal with depression alone was a sign of weakness in men. According to this viewpoint, men should have solved their emotional difficulties by a certain age. Help-seeking was a risky move that could reduce personal control. Men who endorsed this viewpoint commented that long waiting lists discouraged help-seeking and conveyed the view that the problem is not taken seriously.

A total of 9 men did not identify with either viewpoint. However, several statements were endorsed by men in all 3 groups—that depression is a medical condition, people with depression deserve support, and certain cultures discourage help-seeking by pressuring men to be "strong." They did not endorse talking to family or friends about depression or coping by using illicit drugs or alcohol, although many in fact did use these substances.

Discussion: Long waiting lists may have an important impact on help-seeking for men with depression who may have particular difficulty with asking for help. Providing alternate sources of support during the waiting period may indicate to male patients that their depression warrants clinical attention and could improve service use.

House J, Marasli P, Lister M, Brown J: Male views on help-seeking for depression: a Q methodology study. *Psychology and Psychotherapy: Theory, Research and Practice* 2017; doi 10.1111/papt.12144. From King's College London, U.K.; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

Social Skills Training for Psychosis

Social skills training (SST) has small but significant beneficial effects on negative symptoms and other psychopathology in patients with schizophrenia and related disorders, according to the results of a meta-analysis. Contrary to current guidelines in the U.S. and the U.K., SST may deserve wider application, and group SST can be a cost-effective way to address negative symptoms, particularly in resource-limited settings.

Background: SST emerged in the context of deinstitutionalizing patients with psychosis in the 1970s. Since then, it has diversified and grown to assimilate technology and cognitive-behavioral approaches, but according to present guidelines, its usefulness and generalizability are limited. The last major meta-analysis of SST was completed nearly a decade ago. Only recently have clinical trials included negative symptoms as a primary outcome of interest.

Methods: A comprehensive literature search of journals, clinical trial registries, conference abstracts, and dissertations was undertaken to identify randomized controlled trials of SST in patients with schizophrenia, schizoaffective disorder, brief psychotic disorder, or other psychosis. The meta-analysis included 27 studies with a total of 1437 participants. Twenty-five studies applied SST in a group format. The authors classified the types of SST as generic,

cognitive-behavioral SST, social-cognitive skills training, and the UCLA functional adaptive skills training (FAST) program. Control conditions were treatment as usual, active psychological interventions such as CBT, and nondirective supportive counseling.

Results: Overall, SST was significantly more effective for negative symptoms when compared with all comparators and with treatment as usual (effect sizes,* 0.19 and 0.31, respectively; p≤0.01). SST was also more effective than the pooled group of active treatments, but the difference was not significant. However, when the analysis was repeated with successively lower levels of bias risk, effect sizes increased, reaching maximums when only those studies with the lowest bias ratings were included. (See table for most stringent comparison.) SST was also significantly more effective than all comparators pooled at reducing Positive and Negative Syndrome Scale general symptom scores (effect size, 0.32; p=0.02) and at improving social competence (effect size, 0.33; p=0.01), and significantly more effective than treatment as usual at reducing general psychopathology (effect size, 0.40; p=0.007). The available long-term follow-up studies suggest the overall effects of SST are of questionable durability, but improvement in negative symptoms does seem to persist.

Efficacy of SST at Reducing Negative Symptoms

Comparison	# of Studies	Effect Size	Significance
SST vs any comparator	7	0.28	p=0.004
SST vs active comparator	6	0.28	p=0.008
SST vs treatment as usual	5	0.30	p=0.017

Discussion: Although effect sizes in the meta-analysis were not large, antipsychotic medications also have small-to-medium effects on negative symptoms. The results suggest that wider use of SST may be warranted, particularly because the group-based application could offer cost-savings compared with individual psychological therapies.

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

Turner D, McGlanaghy E, Cuijpers P, van der Gaag M, et al: A meta-analysis of social skills training and related interventions for psychosis. *Schizophrenia Bulletin* 2017; doi 10.1093/schbul/sbx146/4618008. From Vrije Universitiet, Amsterdam, the Netherlands; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

***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.

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). The rating checklists are posted at www.alertpubs.com.