

PSYCHIATRY ALERTS NOS

2016 Issue Collection

How to Search: Use Ctrl-F on your keyboard to search the document OR Click on the issue date below to jump to that month's issue or an article title to go directly to the article.

January

Anemia in Psychiatric Patients, 2
Exposure Therapy in OCD, 4
Gestalt-Based Therapy for PTSD, 4
Obsessive-Compulsive Symptoms, 4
rTMS and Smoking Cessation, 5
Suicide Prevention, 1

February

CBT After TBI, 11
CBT: Long-Term Effectiveness, 10
Lavender Oil for Anxiety/Depression, 9
Masculinity and Self-Injury, 8
TNS for Geriatric Depression, 7

March

Adherence Therapy in Schizophrenia, 14
Brain Stimulation and Antipsychotics, 16
Complement Activity in Schizophrenia, 13
Efficacy of Seasonal Depression Treatments, 17
Group Social Rhythm Therapy for PTSD, 15
Markers of Depression in Alzheimer's, 13

April

Aggression and *T. gondii* Infection, 22
CBT for Hoarding, 23
Memory Impairment and Depression, 23
N-acetylcysteine for Skin Picking, 20
Postpartum Relapse in Severe Mental Illness, 20
Suicide Risk After Concussion, 19
Transcutaneous Auricular VNS, 21

May

Depression Biomarker, 26
Depression Prevention for Caregivers, 25
Depression Treatment Guideline, 30
ECT in Late-Life Depression, 27
PTSD Screening in Abused Women, 28
rTMS Recommendations, 29
tDCS for Negative Symptoms, 27

June

Hyperthermia for Depression, 31
Negative Symptom Self-Report, 35
Predicting Antidepressant Nonremission, 32
Psychedelic-Assisted Therapy, 35
Psychotherapy for PTSD, 33

July

ADHD: Adult-Onset, 40
ADHD: Persistent vs. New-Onset, 40
Behavioral Activation Therapy, 37
Brain Stimulation for Generalized Anxiety, 39
Gratitude Writing and Mental Health, 41
Mindfulness Therapy in Depression, 38

August

Blue Light and Manic Symptoms, 45
Brain Stimulation for Alcohol Dependence, 46
Complicated Grief Treatment, 47
Nutraceuticals for Depression, 43
Trauma-Focused Treatment in Psychosis, 44

September

Brain Stimulation for Binge Eating, 49
Depression Guidelines: Psychological Therapy, 53
ECT in Geriatric Depression, 51
Glutamate in Schizophrenia, 50
Social Anxiety Disorder: Online Treatment, 52

October

ACT for Anorexia Nervosa, 57
Hypochondriasis-Related Disorders, 58
Imaging Marker for Bipolar Disorder, 59
Occupational Therapy for Schizophrenia, 55
Open Dialogue Program for Psychosis, 56

November

Curcumin for Depression, 62
Dynamic Psychotherapy for Depression, 65
Lipids in Schizophrenia, 64
Psychosis Risk Calculator, 63
Saffron for Anxious Depression, 61

December

CBT for Resistant Anxiety, 70
OCD: Patient Treatment Preferences, 69
Suicide After Hospital Discharge, 68
Taurine in Psychosis, 71
Virtual Hope Box, 67

2016 Index

PSYCHIATRY ALERTS NOS

Anemia in Psychiatric Patients.....	2
Exposure Therapy in OCD	4
Gestalt-Based Therapy for PTSD.....	4
Obsessive-Compulsive Symptoms.....	3
Reference Guide	6
rTMS and Smoking Cessation	5
Suicide Prevention.....	1

Volume VIII / January 2016 / Number 1

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Suicide Prevention

The World Health Organization recommends that all patients aged >10 years with either a diagnosed mental health disorder or other risk factors should undergo suicide risk assessment that includes evaluation of thoughts and plans of self-harm in the previous month. However, suicide prevention is complicated by the difficulty of accurate prediction and the limited number of effective approaches.

Studies of the epidemiology of suicide in the mentally ill suggest that suicide risk is highest in the first few months after a mental-disorder diagnosis. Risk is also high during inpatient hospitalization, often occurring within the first 3 days after admission. Rates are increased in patients who present to the emergency department with self-harm and in those who have recently made a clinical contact in an acute care setting.

There is no standard of care for suicide risk assessment, and tools for assessment are not very accurate. Guidelines generally recommend collecting information on: previous suicidal behavior; current suicidal thoughts and plans; hopelessness; stressors; symptoms of the mental disorder; impulsivity and self-control; access to highly lethal methods; and protective factors. Risk assessment scales tend to identify a high proportion of false positives, and these patients can then be inappropriately labeled as high-risk and provided with resources they do not need. Conventional suicide risk assessment scales have not been rigorously validated for their ability to predict suicide attempts. Positive predictive values tend to be $\leq 5\%$. Somewhat higher (but still low) positive predictive value has been shown with newer domain-based scales like the Columbia-Suicide Severity Rating Scale. Rule-based methods have used small numbers of statistically validated items. For example, the ReACT self-harm rule is based on 4 variables: recent self-harm, living alone or homeless, cutting as a method of self-harm, and treatment for a current psychiatric disorder. Neurocognitive tests and implicit thoughts of suicide are novel approaches to risk assessment, with little supporting evidence thus far. Clinical guidelines for risk assessment are inconsistent in many ways but

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do consistently recommend assessing risk and protective factors and clarifying the degree of suicidal intent.

Although mental health care can reduce suicide rates, most suicidal people receive no treatment. Identifying and treating depression is a key aspect of suicide prevention. However, antidepressant drugs are often used in self-poisoning, and the relationship of antidepressants to suicidality remains controversial. Lithium and other mood stabilizers may reduce suicide risk. Although there have been no studies of ketamine in suicide prevention, its rapid effect in reducing suicidal thoughts is an attractive feature. Some randomized trials indicate that cognitive behavioral therapy can reduce self-harm or suicide attempts, but suicide is too rare an outcome to study in a clinical trial. Online self-help programs have the advantages of improved access, and reduced costs and stigma.

Bolton J, Gunnell D, Turecki G: Suicide risk assessment and intervention in people with mental illness. *BMJ* 2015; doi 10.1136/bmj.h4978. From the University of Manitoba, Canada; and other institutions. **Funded by the Canadian Institutes of Health Research; and other sources. The authors declared no competing interests.**

Anemia in Chronic Psychiatric Patients

The relationship between psychiatric disorders and anemia is well recognized, but there have been few studies of its prevalence in chronic psychiatric patients. In a cross-sectional study, anemia was present in 25% of patients with chronic psychiatric conditions.

Methods: Hemoglobin levels were assessed in all adult inpatients at a psychiatric hospital over a 1-year period (n=378). Patients were included in the analysis unless they had a significant physical pathology or disease that could affect psychological symptoms or another blood disorder. Using World Health Organization thresholds, anemia was defined as hemoglobin levels of <13 g/dL in adult men and <12 g/dL in nonpregnant women.

Results: Anemia was identified in 96 (25.4%) of the 378 inpatients. Significantly more women than men met criteria for anemia: 35% versus 10% (p<0.001). Mean hemoglobin values did not differ according to age group. Anemia occurred at the highest rate among patients with psychosis (35%), followed by generalized anxiety disorder (32%) and obsessive-compulsive disorder (26%). Prevalence ranged from 22% to 25% for other disorders including depression and bipolar disorder.

Socioeconomic status was associated with anemia: 32% of patients with anemia had low income levels. Medication use was also associated with anemia: 75% of patients with anemia had received psychotropic drugs during the month before hemoglobin was measured; 36% were receiving drugs for a non-psychiatric illness.

Discussion: This study identified a higher prevalence of anemia than studies conducted at other institutions, possibly because the hospital serves a population mainly comprised of patients with severe, treatment-resistant symptoms and high exposure to psychotropic and other drugs. Patients with chronic mental illness usually have a high rate of accompanying medical illness, which can further predispose them to anemia. The prevalence of anemia in patients with a psychotic disorder in this study was particularly high. These patients tend to have poor living conditions and little access to social support; drugs used to treat their illness, such as mood stabilizers and SSRIs, can cause significant hematologic side effects. If untreated, anemia can cause physical symptoms such as fatigue, cognitive dysfunction, and depression, and could complicate the course of existing psychiatric disorders.

Korkmaz S, Yildiz S, Korucu T, Gundogan B, et al: Frequency of anemia in chronic psychiatry patients. *Neuropsychiatric Disease and Treatment* 2015;11:2737–2741. From Firat University, Elazig, Turkey. **Source of funding not stated. The authors declared no competing interests.**

Obsessive-Compulsive Symptoms in Depression

According to a secondary analysis of data from the STAR*D trial, obsessive-compulsive symptoms (OCS) are common in patients with major depression and may interfere with the benefits of antidepressant treatment. Because patients are often reluctant to volunteer information regarding these symptoms, they should be actively evaluated as part of depression treatment.

Methods: The STAR*D trial, which is the largest effectiveness study to date of "real-world" depression, enrolled >4000 patients treated in a stepwise fashion beginning with 12 weeks of open-label citalopram (*Celexa*). All patients were assessed at study entry using the Psychiatric Diagnostic Screening Questionnaire (PDSQ). Those who met diagnostic criteria for obsessive-compulsive disorder on the basis of a clinical interview were not included in the study. The present analysis was based on the OCS subscale of the PDSQ, consisting of 8 items that a patient would endorse if they had experienced obsessive worries or compulsive behaviors within the past 2 weeks. Cutoffs of ≥ 1 and ≥ 4 symptoms were selected to define mild and more severe OCS, respectively. Depression severity was classified according to the 17-item Hamilton Rating Scale for Depression (HAM-D), with cutoffs of < 17 for mild and > 24 for severe. The primary STAR*D outcome was remission, defined as a final HAM-D score of ≤ 7 or a Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR) score of ≤ 5 .

Results: More than half of the sample reported ≥ 1 OCS, and 14% endorsed ≥ 4 . The frequency of both mild and more severe OCS increased with baseline depression severity. (See table.) Compared with those who reported no OCS, patients with ≥ 1 of these symptoms were younger, more severely depressed, more likely to be unemployed, and had more psychiatric comorbidity, physical illnesses, and symptoms of anxious depression.

Overall, depression remitted in 28% of patients after 12 weeks of antidepressant treatment. Likelihood of remission was significantly reduced in patients with OCS. Remission rates on the HAM-D were 31% for patients with no OCS, 25% with ≥ 1 OCS, and 18% with ≥ 4 OCS ($p < 0.001$). Results with the QIDS-SR were similar.

Prevalence and outcomes of OCS in patients with depression		
	≥ 1 OCS	≥ 4 OCS
Depression Severity		
Mild	42%	8%
Moderate	54%	12%
Severe	65%	22%
Odds Ratio* for Remission		
HAM-D	0.85	0.61 [†]
QIDS-SR	0.76 [†]	0.51 ^{††}
† $p < 0.01$ vs. no OCS †† $p < 0.001$ vs. no OCS		

Discussion: These results indicate that OCS are not only common in depression but also that they are infrequently addressed. Causality could not be established because of the study design, but the association likely reflects a feedback loop. Screening depressed patients with a short list of questions based on the PDSQ could help identify those who would benefit from specific treatments for OCS.

Baer L, Trivedi M, Huz I, Rush A, et al; Prevalence and impact of obsessive-compulsive symptoms in depression: a STAR*D report. *Journal of Clinical Psychiatry* 2015;76 (December):1668–1674. From Massachusetts General Hospital, Boston; and other institutions. **The STAR*D study was funded by the NIMH. The present analysis was funded by the Chirag Foundation. Three study authors disclosed financial relationships with commercial sources; the remaining 3 authors declared no competing interests.**

*See Reference Guide.

Exposure Therapy in Refractory OCD

Adjunctive exposure and response prevention (ERP) was an effective treatment for obsessive-compulsive disorder in a group of patients whose symptoms had not responded to an SRI augmented with risperidone (*Risperdal*) or placebo.

Methods: Study participants were adults with a diagnosis of OCD for ≥ 1 year who had experienced a $\leq 25\%$ improvement in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores after a 12-week trial of SRI monotherapy and a further 8 weeks of randomly assigned adjunctive risperidone or placebo. Nonresponders to SRIs plus risperidone were given the option of receiving ERP. Nonresponders to SRIs plus placebo could choose to receive either risperidone or ERP. SRI therapy was continued throughout the ERP study.

ERP was provided in up to 17, twice-weekly, 90-minute sessions that included exposures, daily homework, and telephone check-in. The exact number of sessions was determined by the therapist and patient and was based on improvement. Those who participated in ≥ 10 sessions were designated treatment completers. The primary efficacy outcome was change in the Y-BOCS total score from the start of ERP to the end of ERP 8 weeks later and then at 32-week follow-up.

Results: The group had received a mean of about 2.5 past SRI trials before enrollment in this study. A total of 32 patients completed treatment with risperidone in the randomized trial; of 23 (72%) who were not considered responders, 20 chose to receive ERP. In the group that completed placebo treatment, 14 of 17 (82%) did not experience response; 12 chose to receive ERP, and none chose risperidone. Thus the total ERP sample consisted of 32 patients. Patients completed a mean of 14 ERP sessions, and 25 were treatment completers. Six patients had medication changes during the study.

The mean Y-BOCS total score did not improve significantly during the initial randomized treatment trial with risperidone or placebo. In contrast, scores improved significantly from the start of ERP to the 36-week follow-up ($p < 0.001$; effect size, * 0.52). Scores decreased significantly, from 26 before ERP to 18 at the post-ERP evaluation ($p < 0.001$; effect size, 1.37) and further decreased to 16 at the 32-week follow-up ($p < 0.001$; effect size, 0.54). At post-treatment, 18 participants (56%) were considered responders, and 5 (16%) met criteria for excellent response (Y-BOCS of ≤ 12). At week 32, 17 patients (53%) were considered responders and 11 (34%) achieved excellent response. Patients also showed significant improvement on the Hamilton Rating Scale for Depression over the course of ERP, but not in other secondary outcome measures of social adjustment, insight, or quality of life.

Discussion: In clinical trials, few patients with OCD have achieved an excellent response to SRI therapy alone and many continue to be symptomatic after SRI augmentation. The present study results indicate that ERP is not only effective but acceptable in this patient population.

McLean C, Zandberg L, Van Meter P, Carpenter J, et al: Exposure and response prevention helps adults with obsessive-compulsive disorder who do not respond to pharmacological augmentation strategies. *Journal of Clinical Psychiatry* 2015;76 (December):1653–1657. From the University of Pennsylvania, Philadelphia; and other institutions. **Funded by the NIMH. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

*See Reference Guide.

Gestalt-Based Therapy for PTSD

In a randomized trial, dialogical exposure therapy (DET), a gestalt-based treatment, had comparable effects to a cognitive intervention in adults with posttraumatic stress disorder.

Background: The aim of DET is to restore the continuity of self-concept in patients who have surrendered their sense of self ("self-collapse") as a survival mechanism and continue to cope

using self-collapse during cognitive rehearsals of the traumatic event or when faced with other threats. The therapy used in this study is based on safety and self-acceptance; stabilization; exposure to and confrontation of the trauma via a modification of empty-chair work; and accepting the experience and resulting changes.

Methods: Study participants were 148 treatment-seeking individuals who met DSM-IV criteria for PTSD due to a traumatic event experienced during adulthood. A wide variety of non-military trauma histories were represented, and patients had a moderate-to-severe level of symptoms. Participants were randomly assigned to receive either DET or the control treatment (i.e., cognitive processing therapy [CPT], which is a form of cognitive behavioral therapy with known efficacy in PTSD). DET and CPT were delivered by different groups of therapists, and treatment length was flexible up to a maximum of 24 sessions. The primary outcomes—both self-report measures of PTSD symptom severity: the Impact of Event Scale-Revised (IES-R) and the Post-traumatic Diagnostic Scale (PDS)—were evaluated at the end of therapy and at 6-month follow-up.

Results: Both DET and CPT were associated with improvement in the primary outcome measures immediately after the end of therapy and again at 6 months, with large effect sizes.* (See table.) Differences between therapies were not significant but tended to favor CPT. The largest between-group differences in effect sizes were for posttraumatic cognitions (favoring CPT) and interpersonal functioning (favoring DET). Secondary outcomes—measures of overall psychological functioning and trauma-related cognitions—followed a similar pattern, as did 2 exploratory outcomes: interpersonal problems and life satisfaction. A total of 53% of the DET group and 61% of the CPT group achieved remission (based on PDS scores) post-treatment. At follow-up, remission rates were 60% and 64%, respectively. Rates did not differ statistically between the treatments at either time.

Effect Sizes for Change in PTSD Symptom Severity			
	DET	CPT	Between treatments [†]
Effect size, pre- to post-treatment			
IES-R	1.14	1.57	0.25
PDS	0.93	1.12	0.06
Effect size, pre-treatment to 6-month follow-up			
IES-R	1.33	1.50	0.08
PDS	1.10	1.07	-0.09

[†]Positive effect sizes favor CPT, and negative effect sizes favor DET.

Discussion: Although preliminary, these results suggest that the gestalt-based DET may be a useful alternative to traditional cognitive-based therapies for PTSD. Additional research appears to be warranted.

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

Butollo W, Karl R, Konig J, Rosner R: A randomized controlled clinical trial of dialogical exposure therapy versus cognitive processing therapy for adult outpatients suffering from PTSD after type 1 trauma in adulthood. *Psychotherapy and Psychosomatics* 2015; doi 10.1159/000440726. From Ludwig Maximilian University, Munich, and Catholic University of Eichstatt-Ingolstadt, Germany. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

rTMS and Smoking Cessation

When combined with nicotine replacement therapy, repetitive transcranial magnetic stimulation increased patients' chance of short-term abstinence during the early weeks of a smoking cessation program.

Methods: Study participants were adults (n=37) with high levels of nicotine dependence who had a desire to quit smoking and a history of ≥2 prior cessation attempts. All patients were

provided transdermal nicotine patches and randomly assigned to either rTMS or a sham treatment administered early each day from Monday through Friday for 2 consecutive weeks. rTMS consisted of low-frequency stimulation over the dorsolateral prefrontal cortex, using stimulation parameters that are effective in treating depression and show preliminary evidence of reducing nicotine craving. After 2 weeks, rTMS was stopped and patients continued using the patches at declining doses for another 4 weeks. Smoking cessation was evaluated 6 weeks after treatment completion using self-report and carbon monoxide breath tests.

Results: Abstinence rates after 2 weeks were 89% with nicotine replacement plus rTMS, compared with 50% in the nicotine replacement plus sham group ($p=0.02$). Once rTMS was stopped, relapse rates converged in the groups to 44% and 39% in the groups, respectively, at 6 weeks and to 28% in both groups at 12 weeks. Craving, reported by patients using a visual-analog scale and 2 questionnaires, was significantly decreased 2 weeks after quitting, regardless of treatment assignment.

Discussion: The initial abstinence-promoting effect of rTMS may be clinically useful since smoking cessation is the key objective of many smokers. The effects of rTMS on cigarette craving were less than expected, and the effect on compulsivity, which measures a lack of control, might have reduced the impulse to smoke while experiencing a craving. Future studies should determine stimulation parameters that could extend the length of the rTMS effect.

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

Trojak B, Meille V, Achab S, Lalanne L, et al: Transcranial magnetic stimulation combined with nicotine replacement therapy for smoking cessation: a randomized controlled trial. *Brain Stimulation* 2015;8 (November–December):1168–1174. From the University Hospital of Dijon, France. **Funded by the hospital. The authors declared no conflicts of interest.**

*See Reference Guide.

Reference Guide

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.

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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PSYCHIATRY ALERTS NOS

CBT After TBI	11
CBT: Long-Term Effectiveness	10
Lavender Oil for Anxiety/Depression	9
Masculinity and Self-Injury	8
Reference Guide	12
TNS for Geriatric Depression	7

Volume VIII / February 2016 / Number 2

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TNS for Resistant Geriatric Depression

Trigeminal nerve stimulation significantly improved depression and comorbid anxiety in a small open-label study of geriatric patients with resistant major depressive disorder.¹

Background: TNS is a noninvasive neuromodulatory treatment based on transcutaneous stimulation of the supraorbital branch of the trigeminal nerve. Preliminary studies suggest efficacy in major depression,^{2,3} but safety and efficacy have not previously been studied in geriatric patients.

Methods: Study subjects (n=10; mean age, 73 years; 7 women) were recruited from an out-patient university clinic. All had treatment-resistant depression (≥ 2 failed antidepressant trials) and were experiencing depressive symptoms despite ≥ 4 weeks of current antidepressant therapy, which remained unchanged during the study period. Patients underwent a 10-session TNS protocol that delivered electric stimulation at 120 Hz with a pulse duration of 250 microseconds for 30 minutes each day and were followed for 1 month after completion. The primary outcome was change in depressive symptoms as measured by the Hamilton Rating Scale for Depression (HAM-D). Secondary outcomes were change in anxiety symptoms, which were present in all patients at entry, and in cognitive function.

Results: At baseline, patients had severe depressive symptoms, with a mean HAM-D score of 25. After completion of the TNS protocol, the mean HAM-D score was significantly decreased to 10 ($p < 0.001$), and 8 of the 10 patients (80%) achieved response with a $\geq 50\%$ reduction in HAM-D score. Hamilton Rating Scale for Anxiety scores were also significantly reduced with TNS from a baseline mean of 28 to 12 ($p < 0.001$). Improvements in both depression and anxiety remained stable at 1-month follow-up. TNS did not improve cognitive function. All patients reported mild paresthesia during stimulation at the electrode placement sites, but no serious adverse events occurred. A single patient withdrew from the study for lack of efficacy.

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Discussion: Major depression in elderly patients is typically associated with poor outcomes and high morbidity and mortality. Although the small and open-label nature of this study limit the conclusions that can be drawn, the apparent efficacy and safety of TNS in this population appear to warrant additional study.

¹Trevizol A, Shiozawa P, Cook I, Sato I, et al: Trigeminal nerve stimulation (TNS) for major depressive disorder in the elderly: an open label proof-of-concept trial [letter]. *Brain Stimulation* 2016;9 (January–February):146–147. From Santa Casa School of Medical Sciences, Sao Paulo, Brazil; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

²Schrader L, et al: Trigeminal nerve stimulation in major depressive disorder: first proof of concept in an open pilot trial. *Epilepsy and Behavior* 2011. doi 10.1016/j.yebeh.2011.06.026. See *Psychiatry Alerts NOS* 2011;3 (August):43.

³Cook I, et al: Trigeminal nerve stimulation in major depressive disorder: acute outcomes in an open pilot study. *Epilepsy and Behavior* 2013; doi 10.1016/j.yebeh.2013.05.008. See *Psychiatry Alerts NOS* 2013;5 (July):3.

Masculinity and Self-Injury in Young Adults

Adherence to masculine norms was associated with a modest increase in nonsuicidal self-injury (NSSI) in young adults and with greater use of specific self-injury methods. Since most of the previously known risk factors for NSSI are not modifiable, the present research suggests an area in which it may be possible to intervene to reduce risk.

Background: Masculinity is defined as the dominant set of norms and behaviors that allow men to maintain power and privilege. Previous research has shown an association between depression and self-damaging behaviors, but the specific association of masculinity with NSSI has not been previously examined.

Methods: Study participants were a convenience sample of young adults, aged 18–24 years, recruited from 2 Northeastern U.S. college campuses. Students were invited to participate in an online survey about stress and coping in which they completed the Conformity to Masculine Norms Inventory-22 (CMNI-22), a measure with 11 subscales reflecting such traits as winning, emotional control, risk-taking, and violence. They also completed the Deliberate Self-Harm Inventory and were asked to report how many people they knew who self-injured.

Results: A total of 912 young adults completed the survey. The average age was 20 years, 68% were women, nearly 80% were Caucasian, and about 6% identified as bisexual. A total of 25% engaged in chronic NSSI (defined as ≥ 6 lifetime episodes), with equal rates in men and women. Consistent with previous research, NSSI risk was increased in Caucasians and bisexuals. NSSI was also associated with the number of known self-injurers; those who self-injured knew an average of >4 , and those who did not, an average of 2.

Scores on the CMNI-22 showed a modest but significant correlation with chronic NSSI ($p < 0.05$). Scores were associated with certain methods of self-injury: punching a wall or object in participants of both genders, burning oneself with a lighter or match in men, and preventing wounds from healing in women. In a multivariate model adjusted for known demographic risk factors (e.g., number of self-injurers known and various measures of negative affect), masculinity was associated with increased risk of chronic NSSI (adjusted odds ratio,* 1.05).

Discussion: Results of the present study suggest that adherence to masculine norms and social contagion may both be targets for preventing NSSI. They also suggest that the long-standing gender gap in NSSI prevalence may be closing.

Green J, Kearns J, Ledoux A, Addis M, et al: The association between masculinity and nonsuicidal self-injury. *American Journal of Men's Health* 2015; doi 10.1177/1557988315624508. From the VA Boston Healthcare System, MA; and other institutions. **This study was conducted without funding. The authors declared no competing interests.**

*See Reference Guide.

Lavender Oil for Mixed Anxiety/Depression

Silexan, a lavender oil-based product, improved both depression and anxiety in a randomized trial in patients with mixed anxiety and depressive disorder (MADD).¹

Background: Silexan is patented in Germany as a medical product used for the treatment of "restlessness related to anxious mood". It was previously shown to be effective in generalized anxiety disorder.² Secondary outcomes of other clinical trials suggest it may also have antidepressant effects.

Methods: Study participants, aged 18–65 years, were enrolled from 35 psychiatric practices and met the ICD-10 criteria for MADD, which is based on subsyndromal symptoms of both illnesses. The diagnosis was made by specialized psychiatrists using the World Health Organization's checklist for the disorder. Patients were also required to have a Hamilton Anxiety Rating Scale (HAM-A) score of ≥ 18 . Those who met inclusion criteria ($n=318$) were randomly assigned to treatment with Silexan or a lavender-flavored placebo. Baseline Clinical Global Impression–Severity (CGI-S) scores indicated that half of the patients were at least moderately ill. Primary efficacy outcomes were change from baseline in total scores on the HAM-A and the Montgomery-Asberg Depression Rating Scale (MADRS). Response for each measure was defined as a $\geq 50\%$ decrease in total score, and remission as a score of < 10 for the HAM-A and ≤ 10 for the MADRS.

Results: The study was stopped after an interim analysis showed superior efficacy of Silexan. Mean baseline HAM-A and MADRS scores were 26 and 22, respectively. An interim analysis at 10 weeks found Silexan produced significantly greater decreases in these measures than placebo (see table), and the study was stopped. The secondary outcomes of response and remission did not differ statistically, but favored Silexan numerically. Other secondary outcomes favored Silexan significantly: CGI–Improvement, improvement in daily living skills, and improvement in health-related quality of life. Belching, the only notable adverse effect of Silexan, occurred in 10% of patients. One patient in each group withdrew because of an adverse event.

Change from baseline to week 10 in anxiety and depression, and rates of response and remission			
	Silexan	Placebo	Significance
Total Scores			
HAM-A	-10.8	-8.4	$p=0.02$
MADRS	-9.2	-6.1	$p<0.01$
Response			
HAM-A	42%	35%	NS
MADRS	40%	32%	NS
Remission			
HAM-A	35%	29%	NS
MADRS	47%	34%	$p=0.02$
CGI-I: Much or very much improved	48%	31%	$p<0.01$

Discussion: MADD is not included in the DSM-5 because the proposed criteria were deemed insufficiently reliable. Patients with subsyndromal anxiety and depression often do not receive appropriate treatment, but symptoms can be distressing and disabling and can evolve into a syndromal disorder. Anxiety and depression share a similar vulnerability, which may be related to increased release of glutamate and norepinephrine and variations in serotonin receptor binding. Silexan is a potent inhibitor of the mechanisms that cause release of glutamate and

norepinephrine, blunting the excessive stress response associated with anxiety and depression; and it increases extracellular serotonin levels.

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

¹Kasper S, Volz H-P, Dienel A, Schlafke S: Efficacy of Silexan in mixed anxiety-depression - a randomized, placebo-controlled trial. *European Neuropsychopharmacology* 2005; doi 10.1016/j.euroneuro.2015.12.002. From the Medical University of Vienna, Austria; the Hospital for Psychiatry, Psychotherapy, and Psychosomatic Medicine Schloss Werneck, Germany; and Dr. Willmar Schwabe, GmbH & Co. KG, Karlsruhe, Germany. **Funded by Dr. Willmar Schwabe, GmbH & Co. All study authors declared financial relationships with commercial sources.**

²Kasper S, et al: Lavender oil preparation Silexan is effective in generalized anxiety disorder—a randomized, double-blind comparison to placebo and paroxetine. *International Journal of Neuropsychopharmacology* 2014; doi 10.1017/S1461145714000017. See *Psychiatry Alerts NOS* 2014;6 (February):9–10.

*See Reference Guide.

Long-Term Effectiveness of Adjunctive CBT

Cognitive behavioral therapy, as an adjunct to antidepressant medication, had persistent benefits 3–5 years after treatment in a controlled trial.¹ CBT was also cost-effective, according to standard criteria used in economic analyses.

Methods: Study subjects in the present analysis were U.K. primary-care patients who had participated in a previously reported study of adjunctive CBT. At initial study entry, participants had continued to experience depressive symptoms despite ≥6 weeks of antidepressant medication, with Beck Depression Inventory-II (BDI-II) scores of ≥14. Patients were randomly assigned to receive usual care, which included pharmacotherapy, or to undergo 12–18 sessions of adjunctive CBT. For the present study, patients were contacted 3–5 years after their initial randomization. The primary outcome was the BDI-II score, with response defined as a ≥50% decrease from baseline and remission as a BDI-II score of <10. Secondary assessment measures included quality of life (Short Form health survey 12), depression (Patient Health Questionnaire-9), and anxiety (Generalized Anxiety Disorder 7-item scale). The economic analysis was conducted from the perspective of the National Health Service and personal social services.

Results: A total of 469 patients were randomized in the original study, 396 could be contacted and were invited to participate in the follow-up survey, and 275 completed the questionnaire. The median time to follow-up was 46 months after randomization, which corresponds to 40 months after the end of therapy. At baseline, most patients had at least moderately severe and chronic depression, of ≥2 years’ duration. Three-fourths had a comorbid anxiety disorder, and 80% had ≥1 chronic medical condition.

At follow-up, CBT was associated with a lower mean BDI-II score (19.2 vs. 23.4) and with higher rates of response and remission than usual care. (See table.) The effect size* for the difference in BDI-II scores was 0.45. CBT was also associated with significantly greater improvement in anxiety and self-reported mental but not physical health. More than 70% of patients were still taking antidepressants at follow-up.

Primary and secondary outcomes of adjunctive CBT vs. usual care over an average of 46 months			
	CBT	Usual Care	Odds Ratio*
Response	43%	27%	2.09
Remission	28%	18%	1.77

Total annual health care costs in the CBT group averaged about \$400 more per year than the usual-care group. However, quality of life was improved and the incremental cost is within the limits of accepted social costs in the cost-effectiveness literature.

Editorial.² Evidence of long-term efficacy of depression treatment is a major gap in the psychiatric literature and in clinical practice. Individual CBT is the only psychological treatment with evidence of long-term benefit. The present study suggests the possibility that discontinued CBT may be as effective as continued antidepressant medication and more effective than antidepressants that are discontinued and should be routinely offered to patients with depression who do not have a satisfactory response to antidepressants alone. Unfortunately there is little evidence supporting less intensive forms of CBT, such as group, self-help, or electronic therapies, which may be more widely available.

¹Wiles N, Thomas L, Turner N, Garfield K, et al: Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBaT randomised controlled trial. *Lancet Psychiatry* 2016; doi 10.1016/s2215-0366(15)00495-2. From the University of Bristol, UK; and other institutions. **Funded by the National Institute for Health Research Health Technology Assessment. Two study authors disclosed financial relationships with commercial sources; the remaining 11 authors declared no competing interests.**

²Uher R, Pavlova B: Long-term effects of depression treatment [editorial]. *Lancet Psychiatry* 2016; doi 10.1016/S2215-0366(15)00578-7. From Dalhousie University, Halifax, Canada; and Nova Scotia Health Authority. **The authors declared no competing interests.**

*See Reference Guide.

CBT for Anxiety/Depression After TBI

In a randomized, controlled trial, an adapted form of cognitive behavioral therapy relieved anxiety and depression following a traumatic brain injury. The addition of motivational interviewing to CBT did not enhance its efficacy.

Background: Despite their high prevalence, there has been little research on the treatment of anxiety and depression after TBI. CBT is a preferred psychosocial treatment for anxiety and depression, but following TBI, patients often have impaired memory; attention; executive function; and self-awareness that may limit their ability to benefit from CBT.

Methods: The trial evaluated the effects of adapted CBT (aCBT), which was modified from core CBT to compensate for cognitive impairment. Study participants, recruited from local rehabilitation facilities, were adults with mild-to-severe TBI and either a depressive or anxiety disorder or subsyndromal symptoms that were causing clinical levels of impairment. Patients were randomly assigned to 1 of 3 treatment conditions: aCBT preceded by 3 weeks of motivational interviewing intended to enhance treatment engagement; aCBT preceded by 3 weeks of non-directive counseling as a control; and a wait-list control group that was offered aCBT at the end of 30 weeks of follow-up. The CBT intervention was delivered in 9 weekly sessions followed by 3 booster sessions between 21 and 30 weeks. It included modifications to provide concrete suggestions for cognitive strategies; handouts and summaries; support for planning homework to compensate for executive difficulties; and implementing behavioral changes in vivo where possible. The primary efficacy outcome measures were scores on the Hospital Anxiety and Depression Scale (HADS-Anxiety) and the Depression, Anxiety, and Stress Scale (DASS-Depression). Psychosocial function, a secondary outcome, was measured with the Sydney Psychosocial Reintegration Scale.

Results: The 75 study participants were a mean of nearly 4 years post-injury, and 6 had been injured >10 years in the past. The majority (60%) had comorbid anxiety and depressive disorders, with generalized anxiety disorder and PTSD the most frequent anxiety disorders. All patients assigned to aCBT completed the scheduled treatments. None of the wait-listed controls received off-study therapy before 30 weeks.

Patients in all 3 groups experienced improvement in anxiety and depression over the 30 weeks of follow-up. Compared with baseline, aCBT was associated with small-to-moderate reductions

in anxiety and depression and improved psychosocial function at the post-treatment assessment (9 weeks). After 30 weeks of follow-up, effect sizes * were larger: 0.84 for anxiety, 0.82 for depression, and 0.68 for psychosocial function. Outcomes in patients who received motivational interviewing did not differ from those who received non-directive counseling. Of the combined aCBT groups, 55% moved to a lower category of HADS-Anxiety symptoms by 30 weeks, compared with 33% of wait-listed controls, and 50% of the aCBT groups scored in the normal range. For depression, 66% of the aCBT groups moved to a lower severity category (vs. 20% of the controls), and 48% were in the normal range.

Ponsford J, Lee N, Wong D, McKay A, et al: Efficacy of motivational interviewing and cognitive behavioral therapy for anxiety and depression symptoms following traumatic brain injury. *Psychological Medicine* 2015; doi 10.1017/S0033291715002640. From Monash University, Clayton, Australia; and other institutions. **Funded by the National Health and Medical Research Council, Australia. The authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

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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PSYCHIATRY ALERTS NOS

Adherence Therapy in Schizophrenia	14
Brain Stimulation and Antipsychotics	16
Complement Activity in Schizophrenia	13
Efficacy of Seasonal Depression Treatments	17
Group Social Rhythm Therapy for PTSD	15
Markers of Depression in Alzheimer's	13
Reference Guide	18

Volume VIII / March 2016 / Number 3

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Complement Activity in Development of Schizophrenia

Schizophrenia is a heritable disorder with unknown pathogenic mechanisms. More than 100 human gene loci have been associated with risk of schizophrenia. The strongest association has been with the human leukocyte antigen genes of the major histocompatibility complex (MHC); however, the exact nature of the relationship is unknown. Complement component 4 (C4) genes, which are encoded within the MHC region, were recently investigated as a possible contributor to schizophrenia.

Single nucleotide polymorphism data across the MHC region were analyzed from nearly 29,000 patients with schizophrenia and 36,000 healthy controls from the international Psychiatric Genomics Consortium. Findings indicated that the 2 human C4 genes—C4A and C4B—have distinct relationships with schizophrenia risk, with higher risk associated with increased expression of C4. The authors suggest that excessive complement activity in the brain may contribute to the development of schizophrenia, potentially by causing excessive synaptic pruning in adolescence and early adulthood.

Sekar A, Bialas A, de Rivera H, Davis A, et al: Schizophrenia risk from complex variation of complement component 4. *Nature* 2016; doi 10.1038/nature16549. From Harvard Medical School, Boston, MA; and other institutions. **Funded by the NIH; and other sources. The authors declared no competing interests.**

Neurochemical Markers of Depression in Alzheimer's

According to results of an autopsy-based study, alterations of relaxin receptors may be markers for depression in patients with Alzheimer's disease and should be investigated as potential therapeutic targets.

Background: There is increasing evidence that behavioral and psychological symptoms of dementia (i.e., anxiety, depression, and psychosis) may be the result of neuropathological or neurochemical alterations arising from the degenerative process. As-yet uncharacterized perturbations in multiple transmitter systems may explain the lack of response to conventional

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antidepressants in these patients. Relaxin 3 is a recently identified neuropeptide involved in many aspects of emotional regulation in experimental animals. Of the 2 relaxin 3 receptors, RXFP3 is found throughout the brain and may mediate arousal, stress response, and emotional processing, while RXFP1 occurs throughout the body and has an unclear role in the CNS.

Methods: The present study was conducted to determine whether relaxin family receptors are altered in persons with Alzheimer's disease, with or without depression. Postmortem brain tissues were analyzed from 25 cohort members with Alzheimer's disease who had died during the study, including 13 with depression, and 18 age-matched control subjects with no history of mental illness or neuropsychiatric behaviors. The investigators characterized antibodies to the 2 receptor types with immunoblotting, quantified immunoreactivity in different brain regions, and also assessed the β -amyloid burden in the brains.

Results: Patients with Alzheimer's disease but no depression showed reduced RXFP1 immunoreactivity in the parietal cortex compared with controls, while those with depression did not. Parietal cortex RXFP3 was upregulated only in patients with both Alzheimer's disease and depression. Severity of depressive symptoms was positively correlated with RXFP1 levels but not with RXFP3. Levels of the 2 receptors in patients with Alzheimer's disease were not correlated with dementia severity, the β -amyloid burden, or the use of neuroleptics or sedative-hypnotics during the 8 months before death.

Discussion: Preservation of RXFP1 and upregulation of RXFP3 may be novel neurochemical markers of depression in Alzheimer's disease. RXFP3 agonists are presently available and, based on animal models, may have potential in treating emotional symptoms in dementia.

Lee J, Koh S, Guadagna S, Francis P, et al: Altered relaxin family receptors RXFP1 and RXFP3 in the neocortex of depressed Alzheimer's disease patients. *Psychopharmacology* 2016;233 (February):591–598. From the National University of Singapore; and other institutions. **Funded by the National Medical Research Council of Singapore; and other sources. The authors declared no competing interests.**

Adherence Therapy in Schizophrenia

In a randomized trial, motivational interviewing-based adherence therapy, delivered by community psychiatric nurses, improved medication adherence and symptoms in patients with schizophrenia and poor medication adherence.

Methods: Study subjects were outpatients with any schizophrenia spectrum disorder enrolled in 2 psychiatric nursing services covering large geographical regions of Hong Kong. Participants were required to have schizophrenia onset within the previous 3 years, poor compliance with oral antipsychotic medications, and the mental competence to participate. Eligible patients (n=134; mean age, 29 years) were randomly assigned to receive adherence therapy in addition to usual care or to treatment as usual. Adherence therapy consisted of 6 bi-weekly 2-hour sessions delivered by specially trained nurses during the patient's normally scheduled home visits. Therapy used standard techniques of medication adherence treatment and non-confrontational motivational interviewing techniques. The study had 2 primary efficacy outcomes: adherence, measured with the Adherence Rating Scale (ARS), and scores on the Positive and Negative Syndrome Scale (PANSS). The ARS consists of a single item, scored from 1 (total non-adherence) to 5 (good adherence), as determined by independent ratings from study staff and the patient's nurse. Outcomes were measured at 2 weeks, 6 months, and 18 months after patients completed the 3-month intervention.

Results: At study entry, 85–90% of patients were deemed totally nonadherent or poorly adherent with medication. Compared with treatment as usual, the study therapy was associated with higher rates of adherence and greater symptomatic improvement at the 2-week, 6-month, and 18-month measurement points. By 18 months, average ARS scores increased from a baseline of

1.3 in both groups to 2.5 in the adherence training group and 1.5 in the treatment-as-usual group ($p=0.005$; eta-squared effect size, * 0.30). Mean PANSS scores indicated a significantly lower symptom burden in patients who received adherence therapy, throughout follow-up ($p=0.003$, eta-squared effect size, 0.32), with significant improvement in both positive and negative symptoms. Adherence therapy was associated with improvement in insight into illness and its treatment and with a higher level of functioning. Both groups had a similar number of rehospitalizations overall, but the patients who received therapy had fewer rehospitalizations during the later months of follow-up. They spent fewer days rehospitalized on average—for example, mean 7 versus 15 days during the 4 months before the 18-month follow-up.

Discussion: Unlike other approaches to improving medication adherence, motivational interviewing is a goal-directed, patient-centered style that specifically addresses helping patients resolve ambivalence toward adherence and to understand and cope with the adverse effects of their medication. Results of this study suggest it is effective and can be provided as part of community-based rehabilitation programs.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial, but neither patients nor study nurses were blinded to treatment assignment.

Chen W, Mui J, Gray R, Cheung E: Adherence therapy versus routine psychiatric care for people with schizophrenia spectrum disorders: a randomised controlled trial. *BMC Psychiatry* 2016;16:42. doi 10.1186/s12888-016-0744-6. From the Hong Kong Polytechnic University, Kowloon, China; and other institutions. **Funded by the Government of Hong Kong. The study authors declared no competing interests.**

*See Reference Guide.

Social Rhythm Therapy for PTSD

Group cognitive behavioral social rhythm therapy (CBSRT) may be a promising treatment for veterans with PTSD, depression, and sleep disturbance, according to results of a pilot study.

Background: CBSRT is a manualized treatment that was developed specifically for military veterans, who customarily receive treatment in group therapy in order to extend available resources. Group therapies are also advantageous in PTSD because they promote interpersonal engagement. Social rhythm therapy is based on the premise that stressful life events disrupt normal circadian rhythms, leading to depressed mood and sleep disruption.

Methods: Study participants were 24 male veterans, the majority ($n=17$) from the Vietnam era, who met DSM-IV criteria for both PTSD and major depressive disorder of at least moderate severity and had significant problems with sleep initiation, sleep maintenance, and/or nightmares. Overnight polysomnography was carried out at baseline to rule out severe sleep disorders. Medication use was not an exclusion criteria, provided regimens had been stable for ≥ 6 weeks and remained so throughout the study. Patients received treatment in 1 of 5 groups (median, 5 patients per group). CBSRT consisted of 12 weekly 2-hour sessions that used cognitive-behavioral techniques to establish a consistent routine of daytime and nighttime behaviors. Discussing traumatic events was not the focus of treatment and was avoided. Outcomes were measured at baseline, during treatment weeks 4 and 8, 1 week post-treatment, and 3 months post-treatment. The Daily Sleep Diary was the primary outcome measure of insomnia and nightmares, the 17-item Hamilton Rating Scale for Depression (HAM-D) was the primary depression measure, and the Clinician Administered PTSD Scale for the DSM-IV (CAPS) was the primary PTSD outcome measure. Social rhythms were measured with the Social Rhythm Metric, in which patients recorded the timing of 17 routine daily events.

Results: The majority of patients (88%) completed treatment, and most of the remaining patients completed ≥ 7 of the 12 sessions. Full 3-month follow-up data were available for 19 patients. The majority of patients ($n=18$) were receiving concurrent antidepressant therapy.

Participants experienced significant improvement in all of the sleep indices except for total sleep time. Effect sizes* were 0.72 for sleep onset latency, 0.49 for wake time after sleep onset, 1.09 for number of awakenings, and 1.23 for sleep quality. Frequency of nightmares and nightmare distress were also reduced (effect sizes, 0.83 and 0.64, respectively). Improvements were maintained at 3-month follow-up. Patients also experienced statistically significant improvement in PTSD, with an average weekly reduction of about 2 points in CAPS score. Mean CAPS scores decreased from 75 at baseline to 49 at the post-treatment assessment (effect size, 1.2). Scores continued to improve after treatment completion, although at a slower rate than during treatment. Significant reductions were seen on all 3 CAPS subscales: re-experiencing, avoidance, and hyperarousal ($p < 0.001$). However, only 2 patients achieved a final CAPS score of < 20 , indicating PTSD remission.

Depression symptoms also improved significantly with CBSRT, with mean HAM-D scores decreasing from 21 at baseline to 14 at post-treatment (effect size, 1.01) but worsened somewhat after the end of therapy. A total of 11 patients (46%) experienced a clinically significant reduction in HAM-D score, but only 4 achieved a final score of ≤ 6 , indicating reliable remission of depression.

Scores on the Social Rhythm Metric Index increased significantly over time ($p < 0.001$). This finding indicates that the veterans' daily routines became more consistent over the course of treatment. Improvements in social rhythm consistency were correlated with changes in PTSD symptoms, particularly avoidance, but not changes in depression.

Discussion: Although most of the patients who participated in CBSRT experienced clinically significant reductions in psychiatric symptoms, most did not achieve remission. CBSRT was not designed to be used as monotherapy or to replace gold-standard psychotherapy for PTSD; however, it does appear to be a useful add-on. Efficacy will need to be replicated in other populations (e.g., women, younger veterans) using more rigorous study methods.

Haynes P, Kelly M, Warner L, Quan S, et al: Cognitive behavioral social rhythm group therapy for veterans with post-traumatic stress disorder, depression, and sleep disturbance: results from an open trial. *Journal of Affective Disorders* 2016;192 (March):234–243. From the University of Arizona, Tucson; and other institutions. **Funded by the American Sleep Medicine Foundation; and the Institute for Mental Health Research. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Brain Stimulation and Antipsychotic Drugs

In a preliminary study of patients receiving adequate antipsychotic pharmacotherapy for schizophrenia, transcranial direct current stimulation (tDCS) reduced residual auditory hallucinations. Antipsychotics with high affinity for D2 receptors reduced the beneficial effects of tDCS, but only in women.

Background: Neuroplastic effects of tDCS are dependent upon availability of D2 receptors, which can be blocked by antipsychotic medications. This study was conducted to test the hypothesis that drugs with high affinity for D2 receptors might block the effects of tDCS.

Methods: Study participants were 36 patients (mean age, 33 years; 15 men) with schizophrenia and persistent auditory hallucinations despite ≥ 3 months of adequate antipsychotic drug therapy. Patients were classified according to their antipsychotics' D2 receptor affinity: high (e.g., haloperidol, chlorpromazine, risperidone; $n=11$), low affinity or partial agonists (e.g., clozapine, olanzapine, iloperidone, quetiapine, aripiprazole; $n=12$), or both types of medication ($n=13$). In addition to pharmacotherapy, all patients received twice-daily tDCS for 5 days. The severity of auditory hallucinations was measured with the Psychotic Symptom Rating Scales (PSYRATS).

Results: After 5 days of tDCS treatment, the severity of auditory hallucinations was reduced significantly (effect size, * 1.25; $p < 0.001$; 33% decrease in PSYRATS scores) in the study population. Treatment was also associated with improvement in insight. However, the group receiving high D2-affinity drugs showed the smallest reduction (17% vs. 40% in the other groups). Further analysis revealed that the association between high D2-affinity drugs and diminished clinical effect was limited to women. Antipsychotic drug dose was not correlated with improvement in hallucinations.

Discussion: The improvement in auditory hallucinations and in insight following treatment with tDCS is consistent with previous reports. It is likely that the greater improvement in patients taking low-D2-affinity drugs is due to greater availability of these receptors, allowing the beneficial neuromodulatory effects of tDCS. Estrogen may cause antipsychotics to block these receptors more effectively in women.

Agarwal S, Bose A, Shivakumar V, Narayanaswamy J, et al: Impact of antipsychotic medication on transcranial direct current stimulation (tDCS) effects in schizophrenia patients. *Psychiatry Research* 2015; doi 10.1016/j.psychres.2015.11.042. From the National Institute of Mental Health and Neurosciences, Bangalore, India; and other institutions. **Funded by the Government of India; and other sources. The authors declared no competing interests.**

Common Drug Trade Names: aripiprazole—*Abilify*; clozapine—*Clozaril*; haloperidol—*Haldol*; iloperidone—*Fanapt*; olanzapine—*Zyprexa*; quetiapine—*Seroquel*; risperidone—*Risperdal*

*See Reference Guide.

Long-Term Efficacy of Seasonal Depression Treatments

In a randomized trial, bright light therapy and disorder-specific cognitive behavioral therapy (CBT-SAD) had comparable effects in acute seasonal affective disorder (SAD).¹ Long-term effects over the subsequent 2 winters were significantly better with CBT.²

Methods: Study participants met criteria for a current episode of seasonal depression, based on the Structured Interview Guide for the Hamilton Rating Scale-Seasonal Affective Disorder Version (SIGH-SAD). Those randomly assigned to bright light therapy were instructed to use light boxes daily until they experienced remission of symptoms or until spring. The CBT-SAD treatment group received manualized group therapy based on cognitive restructuring and behavioral activation in 2 weekly sessions for 6 weeks. In the 2 years after acute treatment, participants were contacted by mail in September. Those who had undergone light therapy were encouraged to resume treatment when they experienced a first depressive symptom. The CBT-SAD group members were encouraged to use the principles they had already learned, without the use of a therapist. The primary study outcome was recurrence of depression in the next and second winter, determined in October and December of each year. Participants also attended in-person follow-up visits in January or February.

Results: A total of 177 patients participated in the study, 170 provided follow-up data the next year, and 169 in the second year. Results of acute treatment did not differ in the 2 groups. In the next year, the groups experienced similar rates of SAD recurrence (24–29%) and remission (36–38%). In the second year, rates of remission were significantly higher in the CBT-SAD group (see table), and, although the difference was not significant, more patients in the CBT-SAD group achieved remission. Secondary depression measures also tended to favor CBT-SAD in the second winter.

Depression recurrence and remission in the second year after treatment			
	CBT-SAD	Light Therapy	Significance
SIGH-SAD Recurrence [†]	28%	47%	$p = 0.013$
SIGH-SAD Remission ^{††}	34%	23%	$p = \text{ns}$

[†]SIGH-SAD ≥ 20 and 21-item Hamilton Rating Scale for Depression ≥ 10 and atypical symptom score ≥ 5
^{††} $\geq 50\%$ SIGH-SAD improvement and HAM-D ≤ 7 and atypical symptom score ≤ 7 , or HAM-D ≤ 2 and atypical symptom score ≤ 10

Additional analyses were conducted to explore possible explanations for this pattern. In the CBT-SAD group, participants without recurrence in the next winter were 5 times more likely to go without recurrence in the second, compared with only 2 times more likely in the light therapy group, suggesting greater durability of the effects of CBT-SAD. There was some crossover, with 13% of CBT patients eventually using light therapy in the second winter and a larger number of light therapy patients using psychotherapy. Use of other depression treatments was similar in the 2 groups. Differences between the 2 groups in the second winter could not be attributed to concurrent treatment in general or to any new or ongoing light therapy, antidepressant medication, or psychotherapy.

Discussion: Light therapy is palliative, with effects generally lasting only as long as it is used, and long-term compliance as well as resumption of treatment when necessary is poor. Only one-third of patients in the bright light therapy group followed the recommendation to use the light boxes after the first winter. Given the low rate of continued remission with both treatments over the 3 study years, there is a need to investigate additional approaches to improve long-term results, including maintenance, switch, or combination strategies.

¹Rohan K, et al: Randomized trial of cognitive-behavioral therapy versus light therapy for seasonal affective disorder: acute outcomes. *American Journal of Psychiatry* 2015;172 (September):862–869. See *Psychiatry Alerts NOS* 2015;7 (October):55–56.

²Rohan K, Meyerhoff J, Ho S, Evans M, et al: Outcomes one and two winters following cognitive-behavioral therapy or light therapy for seasonal affective disorder. *American Journal of Psychiatry* 2016;173 (March):244–251. From the University of Vermont, Burlington; and other institutions. **Funded by the NIMH; and other sources. One study author declared financial relationships with commercial sources.**

Reference Guide

Eta-Squared Effect Size: A measure (for use in analysis of variance) of the amount of change in outcome that can be attributed to treatment. It can be interpreted as: 0.02=small; 0.13=medium; and 0.26=large.

Effect Size (Cohen's D): 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 efficacy.

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PSYCHIATRY ALERTS NOS

Aggression and <i>T. gondii</i> Infection	22
CBT for Hoarding.....	23
Memory Impairment and Depression.....	23
<i>N</i> -acetylcysteine for Skin Picking	20
Postpartum Relapse in Severe Mental Illness	20
Reference Guide	24
Suicide Risk After Concussion	19
Transcutaneous Auricular VNS	21

Volume VIII / April 2016 / Number 4

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Concussion and Suicide Risk

In a Canadian population-based study, concussions were associated with a 3-fold increase in the long-term risk of suicide. Risk was further increased in patients whose concussions occurred on a weekend, presumably as a result of recreational rather than occupational injury.

Methods: Claims data were examined for the entire province of Ontario over a 20-year period. The study cohort consisted of adults who had experienced a concussion but were not hospitalized within 2 days of the event (to exclude those with severe traumatic brain injury). Suicides were identified from official death certificates. The data sources also provided information on psychiatric diagnoses, health care utilization, and mechanism of suicide; but much other information was lacking, including social stress, life events, and other suicide risk factors.

Results: More than 235,000 adults experienced a concussion during the 20-year study period. About half of the patients were men, and the mean age was 41 years. A total of 667 suicide deaths occurred over a median follow-up of 9.3 years, equivalent to an annual rate of 31 deaths per 100,000 persons—3 times the population norm. In patients whose injury occurred on a weekend, the suicide rate was 39 per 100,000, about 4 times the population norm. Suicide was associated with additional risk factors: male gender, low socioeconomic status, a prior psychiatric diagnosis, and a prior suicide attempt. Suicide risk was increased as a function of the number of concussions a person experienced.

Discussion: The implications of concussions are often not considered because of the mistaken beliefs that they cannot be identified on medical imaging, do not require follow-up, and that the neurologic symptoms resolve quickly. Information on concussions is not routinely elicited when assessing a patient's history. However, these results suggest that greater attention to long-term care after a concussion could prevent some suicides.

Fralick M, Thiruchelvam D, Tien H, Redelmeier D: Risk of suicide after a concussion. *Canadian Medical Association Journal* 2016; doi 10.1503/cmaj.150790. From the University of Toronto, Canada; and other institutions. **Funded by the Canada Research Chairs program; and other sources. The authors did not include disclosure of potential conflicts of interest.**

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Postpartum Bipolar/Psychotic Relapse

Women with a history of bipolar disorder or a previous episode of postpartum psychosis have a 1 in 3 chance of relapse during the postpartum period, according to results of a meta-analysis.

Methods: A comprehensive literature search identified all English-language studies investigating patients with a diagnosis of bipolar disorder and/or a history of a psychotic or manic episode following childbirth. Included studies (n=37; 5700 deliveries in >4000 women) were longitudinal in design—i.e., cohort studies, randomized controlled trials, or birth register studies. Information about relapse during the year following delivery was obtained. Relapse was defined as emergence of psychosis, mania or hypomania, depression, or a mixed episode; and/or psychiatric hospitalization.

Results: Overall, women with bipolar disorder had a 37% risk of relapse after delivery. Risk did not differ between women with bipolar I and bipolar II disorder. Women with a history of postpartum psychosis had a 31% risk of relapse. Risk was $\geq 50\%$ in women who had a prior history of postpartum bipolar episodes, but the number of women included in these estimates was small. Pharmacotherapy was highly effective at preventing relapse during the postpartum period, both in women with bipolar disorder and in the limited number of women with a history of postpartum psychosis. In both groups, prophylaxis was effective even when it was not started until delivery.

Discussion: Estimates of postpartum relapse risk in the published literature have been highly variable, making it difficult for women with severe mental disorders to plan their pregnancies and relapse-prevention strategies. Accurate estimation of relapse risk is important because overestimation could distress future parents and lead to excessive medication use, reduced rates of breastfeeding, or unnecessarily altered family planning. Underestimation of risk could lead to ineffective relapse-prevention strategies and to delays in referral for specialized perinatal care.

Wesseloo R, Kamperman A, Munk-Olsen T, Pop V, et al: Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis. *American Journal of Psychiatry* 2016;173 (February):117–127. From Erasmus Medical Centre, Rotterdam, the Netherlands; and other institutions. **Funded by the NIMH; and other sources. Four study authors declared financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

Supplement for Compulsive Skin-Picking

N-acetylcysteine, a nonprescription amino-acid supplement, significantly reduced symptoms of excoriation (skin-picking) disorder in a placebo-controlled trial.¹

Background: There is no FDA-approved treatment for excoriation disorder, and no psychological treatment has been clearly effective. *N*-acetylcysteine has 2 potential mechanisms of action in this disorder: It is a cysteine prodrug that increases extracellular glutamate, which may block compulsive behaviors; and its antioxidant properties may confer neuroprotection in the brain. It has also been shown to be effective in patients with trichotillomania,² which is closely related to excoriation disorder.

Methods: Study participants were adults with a primary DSM-5 diagnosis of excoriation disorder. Active treatment consisted of *N*-acetylcysteine started at 1200 mg/day, increased to 2400 mg/day by week 3 and again to the target dosage of 3000 mg/day from week 6 to study end at week 12. Skin-picking symptoms were evaluated in the clinic every 3 weeks. The primary outcome measure was change from baseline in the Yale-Brown Obsessive Compulsive Scale modified for Neurotic Excoriation (NE-YBOCS). This instrument is a 10-item scale assessing picking symptoms during the past 7 days, consisting of 5 items measuring urges and thoughts and 5 items measuring behavior. Secondary outcomes included other symptom measures,

disability, and quality of life, as well as motor inhibition and cognitive flexibility (2 cognitive domains thought to be impaired in persons with excoriation disorder).

Results: A total of 66 patients received randomized treatment: 35 with *N*-acetylcysteine and 31 with placebo. Patients had a mean age of 35 years and had symptom onset at about age 12 years. Nearly 90% were women, about one-third were taking psychotropic medication for other indications, and 85% had never sought treatment for skin-picking. A total of 13 patients did not complete the study, all because of scheduling difficulties.

The *N*-acetylcysteine group showed larger decreases in NE-YBOCS scores than the placebo group, a mean difference of nearly 4 points ($p < 0.05$). *N*-acetylcysteine differed statistically from placebo beginning at the 3-week visit. Effects on the urge/thought subscale were greater with *N*-acetylcysteine than with placebo, but effects on skin-picking behavior were more modest. According to Clinical Global Impression–Improvement ratings, among patients who completed the study, 47% of the *N*-acetylcysteine group and 19% of the placebo group were much or very much improved. Secondary outcome measures, including effects on cognitive function, did not differ between active treatment and placebo. Adverse events of *N*-acetylcysteine were infrequent and mild and included nausea ($n=5$), constipation ($n=2$), dry mouth ($n=1$), and dizziness ($n=1$).

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

¹Grant J, Chamberlain S, Redden S, Leppink E, et al: *N*-acetylcysteine in the treatment of excoriation disorder: a randomized clinical trial. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.0060. From the University of Chicago Pritzker School of Medicine, IL; and other institutions. **Funded by Great American Health; and other sources. Three study authors disclosed financial relationships with commercial sources; the remaining 3 authors declared no competing interests.**

²Grant J, et al: *N*-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. *Archives of General Psychiatry* 2009;66:756–763.

*See Reference Guide.

taVNS for Depression

According to results of a pilot study, transcutaneous auricular vagus nerve stimulation may be an effective noninvasive treatment for depression. The treatment, which uses electrodes applied to the ear, was effective in mild depression, which typically responds poorly to medication, as well as in moderate depression.

Background: Vagus nerve stimulation is an FDA-approved treatment that, because of its invasive nature, is reserved for highly refractory depression. Using the only area on the surface of the body that has afferent vagus nerve distribution, taVNS offers a noninvasive method to deliver treatment.

Methods: Study participants were adults, aged 18–70 years, who met ICD-10 criteria for mild or moderate depression (2 or 3 core symptoms, respectively, plus 2 additional symptoms) and had been psychotropic-free for ≥ 2 weeks. Patients were enrolled and received treatment in 2 cohorts, the first receiving taVNS throughout the 12-week study and the second receiving 4 weeks of sham taVNS before switching to active treatment for 8 weeks. Patients were taught to administer taVNS at home for 30 minutes twice a day. Active taVNS was administered via vagus nerve stimulators that delivered active current to the ear concha. Sham treatment was applied to a part of the outer ear that has no vagus nerve distribution. The primary study outcome was change from baseline to week 4 in Hamilton Rating Scale for Depression (HAM-D) score.

Results: Of 160 participants enrolled in the study (91 in the first cohort, 69 in the second cohort), 148 completed 4 weeks of treatment and 138 completed 12 weeks. A total of 15 patients withdrew from sham treatment because of a lack of effect.

Average baseline HAM-D scores were near 25 in both the active and sham taVNS groups. At the 4-week assessment, HAM-D scores were decreased by 9 points with active taVNS, compared with 3.8 points with sham taVNS ($p < 0.0001$; effect size, * 0.57). When patients were divided into severity subgroups based on initial HAM-D score (mild depression, HAM-D score < 20 ; moderate depression, HAM-D score ≥ 20), both groups showed significant improvement with effect sizes of 0.4 and 0.68 in the mild and moderate groups, respectively ($p = 0.04$ for mild depression, and $p < 0.0001$ for moderate depression). At week 4, there were 24 responders (27%) in the taVNS group and none in the sham treatment group. There were also 3 remissions in the active treatment group. After 12 weeks of treatment, 80% of the first cohort had experienced response and 39% remission. Similar results were observed in the sham treatment group after they switched to active treatment. The only adverse effect of taVNS was exacerbation of pre-existing tinnitus in a few patients.

Discussion: Although preliminary, these results suggest that taVNS may emerge as a first-line treatment for mild-to-moderate depression. Additional study with more rigorous design appears to be warranted.

Rong P, Liu J, Wang L, Liu R, et al: Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: a nonrandomized controlled pilot study. *Journal of Affective Disorders* 2016;195 (May):172–179. From the China Academy of Chinese Medical Sciences, Beijing. **Funded by the National Basic Research Program of China; and other sources. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

***T. gondii* Infection and Aggression**

Evidence of latent *Toxoplasma gondii* infection was associated with aggression in individuals with psychiatric illness.¹

Background: *T. gondii*, a parasite, lives within intracellular structures in the brain of infected hosts and has been linked to several psychiatric illnesses, possibly via low-grade chronic immune activation or anatomic alterations. (The latent infections are common and treatable.)

Methods: This analysis was conducted within a larger study of impulsive aggression in a U.S. population. Study participants included 3 groups: 110 with a lifetime diagnosis of intermittent explosive disorder (IED), 138 with a syndromal psychiatric disorder other than IED, and 110 with no psychiatric illness. Aggression was assessed with the Life History of Aggression Questionnaire, which records aggressive behavior, and the Buss-Perry Aggression Questionnaire, which measures aggression as a personality trait. Other standardized instruments measured impulsivity; lifetime suicidal and self-injurious behavior; and state and trait anger, depression, and anxiety. All participants were assessed for *T. gondii* antibodies after ≥ 4 medication-free weeks.

Results: Of the 358 study participants, 16% were seropositive for *T. gondii*, similar to the seropositivity rate of 14% in the U.S. general population. This included 9% of healthy controls, 17% of psychiatric controls, and 22% of individuals with IED. Seropositive status was associated with the presence of IED ($p = 0.03$ vs. healthy controls), but not with the presence of other psychiatric disorders. Seropositivity was associated with higher composite aggression scores both in an unadjusted model ($p = 0.05$) and after adjustment for impulsivity ($p = 0.011$). Composite impulsivity scores were not associated with seropositivity in an analysis adjusted for aggression. Seropositivity rates were higher in association with syndromal depression, anxiety, and borderline or antisocial personality disorder, but not in individuals with a history of suicide attempt, self-injurious behavior, or substance use disorder.

Discussion: These results suggest a relationship between *T. gondii* and impulsive aggression, both as a dimensional outcome and as a categorical diagnosis. This study may not have been

large enough to detect a relationship with suicidal or self-injurious aggression, which was found in previous research.² Several mechanisms may account for the relationship of *T. gondii* to aggression. Infection may lead to a low-grade chronic state of immune activation, possibly with downstream effects on neurotransmitters involved in aggressive behavior. *T. gondii* cysts may form lesions that alter the anatomy and function of corticolimbic circuits. The infection may also increase expression of genes involved in the production of testosterone, which may be associated with aggression.

¹Coccaro E, Lee R, Groer M, Can A, et al: *Toxoplasma gondii* infection: relationship with aggression in psychiatric subjects. *Journal of Clinical Psychiatry* 2016;77 (March):334–341. From the University of Chicago, IL; and other institutions. **Funded by the NIMH; and other sources. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

²Pedersen M, et al: *Toxoplasma gondii* infection and self-directed violence in mothers. *Archives of General Psychiatry* 2012; doi 10.1001/archgenpsychiatry.2012.668. See *Psychiatry Alerts NOS* 2012;4 (July):40.

CBT for Hoarding Disorder

Preliminary studies indicate that cognitive behavioral therapy (CBT) is effective for hoarding disorder whether the treatment is based on OCD or targeted specifically to hoarding. There is not yet sufficient evidence to compare the relative efficacy of either approach, according to a review.

Generally, treatments for clinically significant hoarding symptoms are the same as those used to treat OCD, most often Exposure and Ritual Prevention (EX/RP). Typical EX/RP programs for OCD consist of 15–20 therapy sessions. For hoarders, exposure may consist of visiting or imagining stores, markets, and other venues that trigger the desire to compulsively acquire things. Through cognitive restructuring, patients learn that anxiety will decrease over time without the use of rituals and that the feared consequences of not hoarding will not occur. Hoarding-specific CBT treatments add motivational interviewing to the techniques of exposure and cognitive restructuring. Since hoarders are not intrinsically motivated by distress over their behavior, additional help is needed from the therapist to motivate change. CBT for hoarding also strives to develop skills such as organization, problem solving, and decision making. Cognitive patterns are addressed by exploring beliefs that may promote hoarding.

A systematic review identified 12 published, peer-reviewed clinical trials of CBT in patients with hoarding disorder. Of these, 6 studies examined traditional CBT techniques, including but not limited to EX/RP. Treatment outcomes were assessed with various versions of the Yale-Brown Obsessive Compulsive Scale. The 2 studies with available effect sizes showed medium-to-large effects. The remaining 6 studies used hoarding-specific CBT. Effect sizes were available from all 5 studies, and ranged from medium to large.

All studies found that hoarding symptoms are difficult to treat. Dropout rates were high, and motivation to participate in treatment was low. EX/RP was helpful, but only partially so. For hoarders who experienced response with EX/RP, effect sizes were large. Effect sizes were smaller for hoarding-specific programs, which are typically longer, requiring about 26 sessions. More research is needed to determine whether hoarding-specific treatment is as effective as EX/RP.

Williams M, Viscusi J: Hoarding disorder and a systematic review of treatment with cognitive behavioral therapy. *Cognitive Behaviour Therapy* 2016;45:93–110. From the University of Louisville and Spalding University, KY. **Source of funding not stated. The authors declared no competing interests.**

Memory Impairment and Depression Recurrence

According to results of a prospective study, residual memory impairment may be a predictive factor for recurrence in patients with remitted depression.

Methods: Study subjects (n=109) with DSM-IV-TR major depressive disorder received treatment at a single hospital and were recruited after they achieved remission. All patients received

antidepressant treatment throughout the study. A comparison group consisted of 211 healthy controls, matched for age, gender, and level of education. Memory function was measured using the logical memory delayed recall subtest of the Wechsler Memory Scale-Revised, which tests recall of a short story immediately after it is told and again after 30 minutes. Patients with depression were divided into 2 groups based on the presence or absence of memory impairment defined as a score ≥ 1 standard deviation below the mean of controls. Patients attended follow-up visits in the clinic every few weeks until their depression returned or the study ended. Recurrence, the primary study outcome, was defined as a Clinical Global Impression–Severity score* of ≥ 4 .

Results: Of the patients with depression, 64 had normal memory function and 45 had memory impairment at study baseline (after achieving depression remission). Patients with memory impairment were older on average than those whose memory was not impaired (55 vs. 45 years; $p < 0.01$), had an older age of depression onset (49 vs. 41 years; $p = 0.01$), and had fewer years of education (13 vs. 14 years; $p = 0.04$). The 2 patient groups did not differ according to gender, number of depressive episodes, total duration of episodes, daily antidepressant dose, or several other factors.

During follow-up, recurrence happened significantly more frequently in the group with memory impairment than in those without (56% vs. 33%; $p = 0.03$). In a multivariate statistical model, memory impairment was associated with a greater risk of recurrence (hazard ratio,* 2.55; $p = 0.006$). Age at onset, number of episodes, family history, and duration of current episode were not associated with risk.

Discussion: Previous research has shown that the number of previous depressive episodes is the most important clinical predictor of recurrence. These results suggest that residual memory impairment may also predict recurrence.

Maeshima H, Baba H, Satomura E, Shimano T, et al: Residual memory impairment in remitted depression may be a predictive factor for recurrence. *Journal of Clinical Psychiatry* 2016;77 (February):247–251. From Juntendo Koshigaya Hospital, Saitama, Japan; and other institutions. **This study was conducted without funding. The authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

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 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.

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

Depression Biomarker	26
Depression Prevention for Caregivers	25
Depression Treatment Guideline.....	30
ECT in Late-Life Depression	27
PTSD Screening in Abused Women.....	28
Reference Guide	30
rTMS Recommendations	29
tDCS for Negative Symptoms	27

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Cognitive Intervention to Prevent Caregiver Depression

A brief cognitive-behavioral intervention was effective in preventing major depression in at-risk nonprofessional caregivers. The protective effects endured through 12 months of follow-up.¹

Background: Depression affects nearly 10% of nonprofessional caregivers, and research shows they have a 4-fold risk of developing depression compared with non-caregivers. Results of a previously published randomized controlled trial indicate that participation in a brief cognitive-behavioral intervention reduced depressive symptoms in caregivers.² The present report details long-term outcomes of this study.

Methods: Participants (n=170) were women acting as the primary caregiver for a dependent family member. All subjects were experiencing depressive symptoms and scored above a cutoff on the Center for Epidemiologic Studies Depression Scale (CES-D), but they did not meet DSM-IV criteria for major depression. The intervention group participated in 5 weekly, 90-minute sessions in groups of about 5 women. Sessions covered education about depression, diaphragmatic breathing, increasing pleasant activities, changing depressive thoughts, and increasing interpersonal contacts. Participants in the control group were encouraged to access services available in the community, and 13% of controls received psychological or psychosocial care. The primary study outcome was the onset of depression, assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) post-treatment and at 1, 3, 6, and 12 months.

Results: Study participants had a mean age of 55 years. About half were caring for a parent, and had been doing so for an average of 10 years. The most common diagnosis of dependents was dementia, which was present in half of patients.

By 12 months, clinical depression had developed in 3 caregivers who received the cognitive-behavioral intervention and in 18 who did not (3% vs. 22%; $p < 0.001$; relative risk,* 0.15). The number needed to treat* to prevent depression onset was 5. Women in the intervention group showed significant reductions compared with baseline in depressive symptoms at post-treatment and each subsequent time point ($p < 0.001$). Depressive symptom scores were lower than

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baseline in the women who received the intervention (effect size,* 1.36 for 12 months vs. baseline). These improvements were significantly greater than those observed in the control group at all time points. Women who underwent the cognitive intervention also had less emotional distress than controls and a lower caregiver burden. Of many factors that were examined as possible mediators of treatment effects, only age was significant, younger caregivers were more likely to benefit.

Discussion: Depression is a major concern in nonprofessional caregivers. Indicated prevention, targeted to people with early symptoms of the disorder, has now been shown to be effective in a few studies using different approaches. The present study suggests a brief cognitive-behavioral intervention can have a strong protective effect. Older caregivers may require more time to process the information in the program and could benefit from more sessions.

¹Vazquez F, Torres A, Blanco V, Otero P, et al: Long-term follow-up of a randomized clinical trial assessing the efficacy of a brief cognitive-behavioral depression prevention intervention for caregivers with elevated depressive symptoms. *American Journal of Geriatric Psychiatry* 2016; doi 10.1016/j.jagp.2016.02.050. From the University of Santiago de Compostela, Spain. **Funded by the Ministry of Labor and Social Affairs of Spain. The study authors declared no financial relationships with commercial sources.**

²Vazquez F, et al: Efficacy of a brief cognitive-behavioral intervention in caregivers with high depressive symptoms. *Behavioral Psychology* 2014;22:79–96.

*See Reference Guide.

Potential Biomarker for Depression

Researchers have identified a metabolite signature, present in peripheral blood mononuclear cells (PBMCs), that appears to accurately distinguish patients with and without depression. The availability of a biomarker for depression could facilitate diagnosis and also increase understanding of the pathogenesis of the disorder.

Methods: Blood samples were collected from 50 first-episode, drug-naive patients with major depressive disorder and 50 demographically matched controls. PBMCs from the 2 groups were compared to identify metabolites that differed between them. The resulting metabolite signature was applied to 58 unselected patients with depression (including 52 receiving medication), 56 healthy controls, and 40 patients with schizophrenia. The latter group was included because there is some symptom overlap between depression and schizophrenia and because schizophrenia is also associated with disturbance of some PBMC metabolites.

Results: The initial analysis identified 17 metabolites that differed between patients with and without depression. Of these metabolites, 8 were involved in neurotransmitter metabolism or energy metabolism. In patients with depression, levels of octanoic acid, hydroxylamine, benzoic acid, γ -aminobutyric acid (GABA), and homoserine were consistently higher than in healthy controls. In addition, levels of malonic acid, isoleucine, lanosterol, valine, sorbitol, creatinine, ribulose 5-phosphate, ethanolamine, malic acid, fumaric acid, γ -tocopherol and dopamine were consistently lower than in healthy controls. The PBMC signature was also highly accurate in the independent validation sample distinguishing patients with depression from healthy controls.

Discussion: PBMCs offer direct information about altered cellular pathways and may be a valid surrogate of brain function. Depression-related metabolic alterations have also been identified using other, less accessible body tissues. The accuracy of the PBMC signature was comparable to these previously identified biomarkers. Combined with other findings, the results of this study suggest depression may involve disturbed glutamate, deficiency of central dopamine, a decrease of excitatory neurotransmitters, and increased GABA. The results also suggest depression is related to a deficiency of circulating glucose levels.

Zheng P, Fang Z, Xu X-J, Liu M-L, et al: Metabolite signature for diagnosing major depressive disorder in peripheral blood mononuclear cells. *Journal of Affective Disorders* 2016;195 (May):75–81. From the First Affiliated Hospital of Chongqing Medical University, China; and other institutions. **Funded by the National Natural Science Foundation of China. The authors did not include disclosure of potential conflicts of interest.**

Cognitive Effects of ECT in Late-Life Depression

The cognitive adverse effects of ECT in patients with late-life depression appear to be limited and transient, according to a systematic review. Other forms of brain stimulation appear to have beneficial effects on cognition but have not been studied in elderly patients.

Methods: A literature search was undertaken to identify all published articles describing the cognitive effects of any form of brain stimulation to treat depression in patients aged >65 years. Of 42 publications identified, 32 were comparative studies of the effects of ECT, 7 were case reports, and 3 were studies of other forms of brain stimulation. The latter 3 studies, of repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS), were too few and of too poor methodologic quality to include in the systematic review.

Results: Overall, the literature does not provide convincing evidence that ECT is associated with clinically significant lasting cognitive deficits in late-life depression. Cognitive deficits due to ECT seem to be confined to the acute course of therapy and the immediate post-treatment period. These transient impairments involve orientation, attention, and processing speed and appear to be more pronounced in patients with late-life depression and comorbid dementia. Global measures of cognition generally show full recovery or improvement at the completion of ECT. Studies also suggest cognitive outcomes are better with right unilateral ECT than with bilateral treatment. To date, the effects of ultra-brief pulse ECT, focal electrically administered seizure therapy, and magnetic seizure therapy have not been investigated in older patients.

Kumar S, Mulsant B, Liu A, Blumberger D, et al: Systematic review of cognitive effects of electroconvulsive therapy in late-life depression. *American Journal of Geriatric Psychiatry* 2016; doi 10.1016/j.jagp.2016.02.053. From the University of Toronto, Canada; and other institutions. **Funded by the Centre for Addiction and Mental Health. Five of 6 authors disclosed potential conflicts of interest.**

Transcranial Stimulation for Negative Symptoms

In a proof-of-concept randomized trial, prefrontal transcranial direct current stimulation (tDCS) improved negative symptoms in a group of patients with schizophrenia.

Methods: The study enrolled 20 patients (mean age, 36 years; 5 women) with paranoid or disorganized schizophrenia according to DSM-IV criteria. Participants were required to have predominant negative symptoms, a Positive and Negative Syndrome Scale (PANSS) score of >70, and a stable antipsychotic regimen for >4 weeks. In addition to their antipsychotic medication, which remained unchanged during the study, participants were randomly assigned to receive double-blind active or sham tDCS in 20-minute sessions on 10 consecutive weekdays. Treatment was delivered using a direct current stimulator with the anode over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right orbitofrontal region. Assessment was carried out at baseline, immediately after the 5th and 10th treatments, and at 4 weeks (2 weeks after the 10th/final treatment). The primary outcome was change from baseline in the Scale for the Assessment of Negative Symptoms (SANS). Functional MRI studies were conducted in a subgroup of 16 patients to characterize the effects of tDCS on brain activation patterns.

Results: Active tDCS was associated with a 36% decrease in the SANS total score from baseline to final assessment, compared with a <1% change in the control group (p=0.008). The 2 groups differed statistically by the first assessment after 1 week of treatment (p<0.05). No significant effects were detected for gender, age at onset, or handedness. Of the 5 SANS subscales, only alogia showed a significant decrease with active tDCS (41% vs. 7% with sham treatment; p=0.03).

Active tDCS was also associated with significant improvement in some secondary outcomes (see table, next page), including the PANSS total and negative symptom scores; the Calgary

Depression Scale for Schizophrenia (CDSS); and the Subjective Well-being under Neuroleptic Treatment Scale (SWN). Other tests of cognitive function and subjective well-being showed no differences between groups. Functional MRI studies showed acute treatment effects on connectivity in the left DLPFC and subgenual cortex, areas previously identified by these researchers as affected by tDCS in healthy subjects.

Clinical Outcomes of Active vs. Sham tDCS			
	Active tDCS	Sham tDCS	Significance
SANS score–baseline	60	64	p=ns
SANS score–after week 4	38	64	p=0.008
PANSS total score–baseline	80	86	p=ns
PANSS total score–after week 4	61	84	p=0.011
PANSS negative symptom score–baseline	24	25	p=ns
PANSS negative symptom score–after week 4	17	27	p=0.001
CDSS–baseline	6	8.9	p=ns
CDSS–after week 4	3	6	p=0.042
SWN–baseline	83	73	p=ns
SWN–after week 4	95	73	p=0.033

Discussion: Negative symptoms are particularly difficult to treat and are associated with poor outcomes. These encouraging preliminary results suggest that adding tDCS to stable antipsychotic pharmacotherapy may be an effective option and that further study is warranted.

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

Palm U, Keeser D, Hasan A, Kupka M, et al: Prefrontal transcranial direct current stimulation for treatment of schizophrenia with predominant negative symptoms: a double-blind, sham-controlled proof-of-concept study. *Schizophrenia Bulletin* 2016. doi 10.1093/schbul/sbw041. From Ludwig Maximilian University and the University of Applied Sciences, Munich, Germany. **Funded by Ludwig Maximilian University; and the Federal Ministry of Education and Research. Three study authors disclosed financial relationships with commercial sources; the remaining 9 authors declared no competing interests.**

*See Reference Guide.

Questionnaire for PTSD Risk in Abused Women

A new brief screening questionnaire was able to identify increased risk for PTSD in a study of women reporting partner abuse.

Methods: The questionnaire was developed with the help of women participating in a 7-year longitudinal study of domestic-abuse survivors. Participants were recruited after they sought assistance for domestic abuse. Women were interviewed using 8 different freely available questionnaires covering PTSD symptoms; severity of abuse; adverse childhood experiences; self-efficacy; safety behavior; and social support and connectedness. A total of 16 different items were selected a priori and assessed for their ability to predict clinical levels of PTSD symptoms within 8 months after the initial contact. A list of predictive items was developed and then validated by applying it to the same subjects 16 months after baseline.

Results: A total of 300 women participated in the questionnaire development, of whom 289 (96%) were available for the full 16 months. Women had a mean age of 31 years (range, 18–52 years) and had an average of 2 children.

Of the 16 items evaluated, 4 were identified as positive predictors of PTSD at 8 months: baseline PTSD symptoms count, adverse childhood experiences, emotional support, and general self-efficacy. Of the 23 women in the lowest of 5 risk categories, none had PTSD symptoms at 8 months and 2 had symptoms at 16 months. Of the 35 women in the highest risk category, 29 (83%) had PTSD at 8 months and 21 (60%) at 16 months.

Discussion: This questionnaire was developed to meet the need identified by the NIMH to identify trauma survivors at the greatest risk of sustained PTSD and is available as part of the published open-access article at <http://online.liebertpub.com/doi/full/10.1089/jwh.2015.5287>. The questionnaire was developed in a narrowly defined population but is likely to be useful in other groups, such as those identified through clinical screening (rather than self-identifying). Screening of women for partner violence is recommended, but there has been little direction on how to help those with positive screens. The questionnaire may help identify those who should be referred for mental health and other services.

Symes L, Maddoux J, McFarlane J, Pennings J: A risk assessment tool to predict sustained PTSD symptoms among women reporting abuse. *Journal of Women's Health* 2016;25 (April):340-357. From Texas Woman's University, Houston; and Elite Research, LLC, Carrollton, TX. **Funded by the Houston Endowment; and Texas Woman's University. The authors declared no competing interests.**

Recommendations for rTMS in Depression

The Clinical TMS Society recommends repetitive transcranial magnetic stimulation for patients whose depression has failed to respond to ≥ 1 antidepressant trial. rTMS can be used with or without concomitant antidepressants, and there is no evidence of increased risk of adverse events if the 2 are combined. In addition, rTMS is also endorsed as an acute treatment for depression by organizations including the American Psychiatric Association and the Agency for Healthcare Research and Quality.

The Clinical TMS Society has issued recommendations pertaining to clinicians at rTMS clinics. In addition to the specific clinical recommendations (see box), they include general information regarding the education of providers, the responsibility of the attending physician for managing the treatment team, obtaining informed consent, and evaluating outcomes. Safety issues such as the need for staff to have CPR or basic life support training and the ability to manage seizures, a rare (about 1 per 30,000 treatment sessions) but major safety concern are also included. While emergency medical services should be accessible, availability of IV access, cardiac defibrillators, suction, and oxygen are not necessary to deliver rTMS safely.

Based on the literature and clinical consensus, the standard treatment plan is for a specified parameter set of high-frequency left prefrontal rTMS delivered in 5 daily treatments over 4–6 weeks. Patients who are slow responders may benefit from an additional 1–4 weeks of treatment, and 12 weeks of twice-weekly continuation treatment may produce additional responses. An extended treatment course is further justified by the absence of any known cumulative toxicity. Most polled TMS providers recommended continuing previous medications during rTMS therapy and refraining from medication taper during an acute rTMS course. Once the patient has had the maximum benefit, treatment should be tapered and a continuation and maintenance regimen should be planned. In addition, most polled clinicians used concomitant maintenance medications and psychotherapy; continuation or maintenance rTMS may be used if other

Recommendation 1: TMS therapy is recommended as an acute treatment for symptomatic relief of depression in the indicated patient population.

Recommendation 2: TMS therapy is recommended for use as a subsequent option in patients who previously benefited from an acute treatment course and are experiencing a recurrence of their illness (continuation or maintenance).

Recommendation 3: TMS therapy can be administered with or without the concomitant administration of antidepressant or other psychotropic medications.

Recommendation 4: TMS therapy can be used as a continuation or maintenance treatment for patients who benefit from an acute course.

Recommendation 5: TMS therapy can be reintroduced in patients who are relapsing into depression after initially responding to TMS treatment.

treatments are unsuccessful or if a patient has a history of frequent relapses. These sessions may be administered one at a time on a monthly, biweekly, or weekly basis, or as needed by the patient.

Perera T, George M, Grammer G, Janicak P, et al: The Clinical TMS Society consensus review and treatment recommendations for TMS therapy for major depressive disorder. *Brain Stimulation* 2016; doi 10.1016/j.brs.2016.03.010. From Contemporary Care, Greenwich, CT; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

ACP Guideline: Treating Depression

According to a new guideline from the American College of Physicians (ACP), either cognitive behavioral therapy (CBT) or second-generation antidepressants can be recommended to treat major depressive disorder after discussing treatment effects, adverse-effect profiles, costs, accessibility, and preferences with the patient.

The guideline is meant to be used for the treatment of major depression in adults and is based on a systematic evidence review sponsored by the Agency for Healthcare Research and Quality. The review included randomized clinical trials, other systematic reviews, and meta-analyses of CBT, SSRIs, SNRIs, bupropion, mirtazapine, nefazodone, and trazodone published between 1990 and September 2015. Evidence on the harms of treatment also included observational studies. First-generation antidepressants were not reviewed because they are rarely used.

The ACP panel concluded that moderate evidence suggests second-generation antidepressants and CBT are equally effective as monotherapy after 8–52 weeks. Low-quality evidence provides little support for combining the treatments. Conflicting evidence suggests there may be a slight increase in treatment discontinuation with antidepressants, compared with CBT. Harms associated with antidepressant medications are likely to have been underrepresented in the included trials, and CBT probably has fewer adverse effects than medication. CBT is also associated with lower relapse rates than antidepressant therapy. In patients whose depression does not respond to an antidepressant, there is little evidence to support the options of switching among drugs, augmentation with another drug, or switching to or augmenting with CBT.

Qaseem A, Barry M, Kansagara D, for the Clinical Guidelines Committee of the American College of Physicians: Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine* 2016;164 (March 1):350–359. From the American College of Physicians, Philadelphia, PA, and other institutions. **Funded by the American College of Physicians. Three study authors disclosed financial relationships with commercial sources.**

Common Drug Trade Names: bupropion—*Wellbutrin*; mirtazapine—*Remeron*; nefazodone—*Serzone*; trazodone—*Desyrel*

Reference Guide

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

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PSYCHIATRY ALERTS NOS

Hyperthermia for Depression	31
Negative Symptom Self-Report	35
Predicting Antidepressant Nonremission	32
Psychedelic-Assisted Therapy	35
Psychotherapy for PTSD	33
Reference Guide	36

Volume VIII / June 2016 / Number 6

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Whole-Body Hyperthermia for Depression

In a randomized trial, a single treatment with whole-body hyperthermia (WBH) had rapid and lasting antidepressant effects in a small group of patients.¹

Background: Efficacy of WBH was previously demonstrated by several of the present study authors in an uncontrolled study in 16 depressed adults.² The present controlled trial was undertaken to replicate the initial results.

Methods: Study subjects, aged 18–65 years (n=34), were recruited from advertising and social media, not referred clinically. They were required to have been experiencing depression for ≥4 weeks and to have a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥16. Patients taking antidepressants were excluded, as were those whose symptoms decreased by ≥30% between screening and the baseline assessment. Subjects were randomly assigned to a single session of real or sham WBH, with continuous monitoring of core and skin temperatures and heart rate. In the active WBH group, heat was delivered by infrared lights at the level of the chest and by infrared heating coils at the level of the legs until the core temperature reached 101.3 degrees, the upper limit for mild-intensity treatment. Treatment time varied, averaging 107 minutes (range, 81–140 minutes). The sham treatment was delivered with the same equipment, providing only nonheating light and noise to mimic active treatment. The primary study outcome measure was the HAM-D, assessed at 1, 2, 4, and 6 weeks.

Results: A total of 16 patients underwent active WBH, and 14 had sham treatment. Ten of the 14 patients in the sham group believed they had received active treatment. Patients had baseline HAM-D scores averaging in the low 20s.

Mean reductions in HAM-D score were significantly greater among participants who received WBH than those who received sham treatment. (See table, next page.) Although participants who received WBH reported more sweating and nausea than the sham group immediately after the treatment, no other adverse effects were observed.

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HAM-D scores in patients receiving real vs. sham WBH				
	Mean HAM-D Score		Significance	Effect Size*
	WBH	Sham		
Baseline	(n=16) 20.7	(n=14) 22.8	p=ns	—
Week 1	(n=15) 14.8	(n=14) 20.9	p<0.001	2.23
Week 2	(n=15) 12.7	(n=12) 18.7	p=0.001	2.11
Week 4	(n=15) 12.9	(n=11) 17.8	p=0.02	1.66
Week 6	(n=15) 12.4	(n=11) 17.8	p=0.02	1.66

As shown by the change in HAM-D scores, active improvement occurred only in the first 2 weeks following WBH treatment, after which time scores remained stable. Rates of response, defined as a $\geq 50\%$ decrease from baseline HAM-D score, were 60% with active treatment and 7% with sham treatment. Remission, defined as a HAM-D score ≤ 7 , was achieved by 40% of the active treatment group and by none of the sham group.

Discussion: Pleasant thermal signals of warmth are transmitted via neural pathways that may be involved in depression and that show decreased activity in patients with depression who have also shown abnormalities in thermoregulation characterized by increased core body temperatures and reduced ability to sweat. These reportedly normalize after successful treatment. Although response and remission rates in this study were lower than those observed in antidepressant pharmacotherapy trials, the results suggest that WBH could be a safe and effective alternative to medication.

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

¹Janssen C, Lowry C, Mehl M, Allen J, et al: Whole-body hyperthermia for the treatment of major depressive disorder: a randomized clinical trial. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.1031. From the University of Wisconsin-Madison; and other institutions. **Funded by the Brain & Behavior Research Foundation; and other sources. One study author disclosed a financial relationship with a commercial source; the remaining 15 authors declared no competing interests.**

²Hanusch K, et al: Whole-body hyperthermia for the treatment of major depression: associations with thermoregulatory cooling. *American Journal of Psychiatry* 2013;170 (July):802–804. See *Psychiatry Alerts NOS* 2013;5 (October):58.

*See Reference Guide.

Imaging to Predict Antidepressant Nonremission

A brain imaging biomarker accurately identified a subgroup of patients with depression who did not experience remission after 8 weeks of medication.

Background: Diffusion tensor imaging (DTI) is an MRI technique that measures connectivity in brain circuitry and can identify white matter tracts that are relevant to depression. In previous work, the investigators found functional alterations in 2 white matter tracts relevant to antidepressant response: increased activity in the cingulate portion of the cingulum bundle (CgC) and reduced activity in the stria terminalis. In the present study, they tested the ratio of activity in these 2 tracts as a biomarker to predict nonremission.

Methods: Participants were patients with nonpsychotic major depressive disorder who were either medication-naïve or had a washout of prior medications and had not used any of the

study drugs in the present depressive episode. Patients were randomly assigned to 8 weeks of open-label treatment with escitalopram, sertraline, or extended-release venlafaxine and could receive no psychotherapy or other alternative treatment. Remission was defined as a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≤ 7 . DTI was acquired at baseline by MRI. For the ratio, a threshold value of 1 was used because it is about 1 standard deviation higher than the ratio in normal subjects. The proportion of remitters was characterized in a test cohort of 74 patients and in a replication cohort of 83 patients.

Results: There were 40 nonremitters (54%) in the test cohort and 63 nonremitters (75%) in the replication cohort. Remitters were younger and had shorter disease duration than nonremitters in the test cohort. In the replication cohort, remitters and nonremitters did not differ clinically or demographically.

Using the cutoff ratio of 1, the DTI biomarker identified 15 of 40 (38%) nonremitters and 2 of 34 (6%) remitters in the test cohort, corresponding to an accuracy of 88%. The accuracy was 100% for escitalopram and sertraline and 75% for venlafaxine. In the replication cohort, the marker selected 15 of 63 (24%) nonremitters and 3 of 20 (15%) remitters, for an accuracy of 83%. Accuracy in the replication cohort was 83% for escitalopram, 100% for sertraline, and 75% for venlafaxine. Pooled data from both cohorts showed 95% accuracy with the SSRIs and somewhat lower accuracy for venlafaxine.

Discussion: While there are many effective antidepressants available, currently no pretreatment measures exist to aid in selecting from among the options. Correctly identifying patients unlikely to achieve remission with the 3 most commonly prescribed antidepressants could lead to earlier initiation of alternate treatments (e.g., polypharmacy, CBT, ECT), hastening response.

Grieve S, Korgaonkar M, Gordon E, Williams L, et al: Prediction of nonremission to antidepressant therapy using diffusion tensor imaging. *Journal of Clinical Psychiatry* 2016;77 (April):e436–e443. From Sydney Medical School—Westmead and Westmead Millennium Institute, Sydney, Australia; and other institutions including Brain Resource, Sydney and San Francisco, CA. **Funded by Brain Resource Ltd. Four study authors disclosed financial relationships with commercial sources including Brain Resource Ltd; the remaining author declared no competing interests.**

Common Drug Trade Names: escitalopram—*Lexapro*; sertraline—*Zoloft*; venlafaxine, extended release—*Effexor XR*

Trauma-Focused Therapies for PTSD

According to results of a comprehensive systematic review and meta-analysis, trauma-focused psychotherapies (TFPs) are superior to pharmacotherapy and should be regarded as first-line treatment for PTSD.

Background: Treatment guidelines for PTSD offer contradicting recommendations for use of medication or psychotherapy as the first-line of treatment. For example, the American Psychiatric Association and the U.S. Department of Veterans Affairs guidelines indicate that medication and psychotherapy are equally effective and either can be used as first-line treatment. In contrast, the World Health Organization (WHO) and the U.K.'s National Institute for Clinical Excellence consider TFPs to be more effective than pharmacotherapy and recommend against medication when trauma-focused therapies are available.

Methods: A comprehensive literature search identified all available randomized trials, published and unpublished, comparing any therapy with an active or placebo control in adults with PTSD. The analysis included only trials that met criteria for minimum adequacy: 8 weeks of medication or 8 sessions of psychotherapy. Therapy sessions had to be individual, in-person, and manualized. Therapies were only compared with an active control, not a wait list or treatment as usual, to minimize bias from nonspecific social effects of participation. Therapy studies that included adjunctive medication were included, as long as the adjunctive medication was similar in both treatment and control groups. Psychotherapy controls were supportive therapy, biofeedback, and relaxation training. All medication studies had placebo controls. Comorbid

disorders were permitted, but studies whose entire population had a specific comorbidity were excluded. The analysis included studies of acute treatment (8–12 weeks), and those with intermediate (14–27 weeks) durations, as well as longer-term studies with maintenance and relapse-prevention designs. Study outcomes could be any gold-standard interview-based measurement.

Results: The analysis included 55 studies enrolling a total of 6313 patients, of whom 49% were women and 40% were military veterans. Average treatment duration was 18 weeks (range, 8–104 weeks). Most studies had important limitations or biases. Psychotherapy trials, although generally better designed than drug trials and rated at low risk of bias, could not be double-blind. Of 31 medication trials, 72% were industry supported and most were rated as high or very high risk of bias.

Studies that compared change from baseline in PTSD symptoms found large effects for both medications and psychotherapy. Effects generally increased over time. Effect sizes* were larger for psychotherapy, ranging from 0.95 for acute interpersonal psychotherapy to 8.6 for cognitive processing therapy at ≥34 weeks, compared with a range of 0.86–3.8 for pharmacotherapy. Adjunctive pharmacotherapy showed no benefit. Studies that compared active treatments with controls found several TFPs significantly outperformed both medications and non-TFP psychotherapies. (See table.) Medications with large effect sizes were sertraline, venlafaxine, and nefazodone. Many other drugs and drug classes, including antipsychotics, anticonvulsants, and most SSRIs, showed no effect, or effects too small to outweigh potential harms and high risk of study bias. Prazosin was the only effective adjunctive pharmacotherapy.

TFPs that significantly outperformed control treatments			
	Effect Size at 8–12 Weeks	Effect Size at 14–27 Weeks	Effect Size at ≥34 Weeks
Cognitive processing therapy	1.08	1.22	0.57
Eye movement desensitization reprocessing	0.87	Not evaluated	1.12
Prolonged exposure/imaginal exposure	1.01	1.03	0.80
Stress inoculation training	1.26	0.4	Not evaluated

When the 6 major current treatment guidelines were compared with the results of this analysis, only 3 were in agreement: the National Institute for Clinical Excellence, the Australian, and the WHO guidelines.

Discussion: Psychotherapy should be first-line treatment for PTSD, not only because of superior efficacy but also because the effects persist long after therapy completion, unlike medications, which must continue to be taken. These study results suggest medications work by blunting expression of PTSD symptoms and do not affect underlying processes. Working directly with trauma appears to lead to better outcomes. For patients who cannot engage in psychotherapy, sertraline or venlafaxine may be helpful. The common U.S. practices of prescribing SSRIs, SNRIs, anticonvulsants, and antipsychotics should be avoided, as should polypharmacy.

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

Lee D, Schnitzlein C, Wolf J, Vythilingham M, et al: Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systemic review and meta-analyses to determine first-line treatments. *Depression and Anxiety* 2016; doi 10.1002/da.22511. From JBSA (Joint Base San Antonio) Fort Sam Houston, San Antonio, Texas; and other institutions. **Source of funding not stated. One study author disclosed a financial relationship with a commercial source; the remaining 5 authors declared no competing interests.**

Common Drug Trade Names: nefazodone—*Serzone*; prazosin—*Minipress*; sertraline—*Zoloft*; venlafaxine—*Effexor*

*See Reference Guide.

Psychedelic Drug-Assisted Therapy

According to a literature review, psychedelic drugs, used in conjunction with psychotherapy, have the potential to profoundly alter the course of some mental illnesses.

In the model of psychedelic-assisted treatment, the drug is used once or a few times during hours-long psychotherapy sessions to overcome obstacles to successful therapy and catalyze a therapeutic experience. Areas where this approach has shown promise include obsessive-compulsive disorder, cancer anxiety, substance-use disorders, and PTSD. Psilocybin and 3,4-methylenedioxy-methamphetamine (MDMA) have been investigated in clinical trials, albeit with small sample sizes, that were conducted at major U.S. universities, with FDA approval. Several studies have been published, and many others are in progress.

The hallucinogen psilocybin was recently studied at Harbor-UCLA Medical Center in 12 patients with advanced cancer and anxiety. Patients received 2 psychotherapy sessions, 1 month apart—1 with psilocybin and 1 with placebo, in random order. Patients were carefully screened and prepared during several sessions before the treatment. Use of psilocybin was safe, and patients experienced significant relief of anxiety and depressed mood. Similar, larger-scale studies are now underway at Johns Hopkins University and New York University. Screened, healthy subjects given psilocybin in a controlled environment have reliably experienced a sense of unity, transcendence of time and space, and positive mood. These effects confer a renewed and long-lasting sense of purpose and meaning and may provide a potentially valuable therapeutic intervention for such difficult-to-treat conditions as end-of-life anxiety and alcoholism. Ongoing or recently completed studies of psilocybin-assisted psychotherapy involve patients with OCD, cancer anxiety, tobacco addiction, cocaine use, and alcohol dependence.

Early reports suggest MDMA has potential for treating PTSD. It allows patients to remember and discuss thoughts and feelings that are usually accompanied by fear and anxiety. Recently, results of 2 placebo-controlled phase II trials supported its efficacy in PTSD refractory to other treatments, and more trials are underway. The drug has a half-life of about 8 hours and has typically been used during 8-hour therapy sessions combining periods of inner focus with periods of interaction with the therapist. In addition to improvement in PTSD symptoms, many patients also report deeply meaningful therapeutic experiences and lasting improvements in different areas of their lives. Extensive research has been conducted on the potential negative effects of MDMA in recreational users and healthy volunteers. The studies did not uncover any risks that would be relevant with 1 or a few occasions of use in a therapeutic setting.

Mithoefer M, Grob C, Brewerton T: Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA. *Lancet Psychiatry* 2016; doi 10.1016/s2215-0366(15)00576-3. From the Medical University of South Carolina, Charleston; and Harbor-UCLA Medical Center/Los Angeles BioMedical Research Institute, Torrance, CA. **Source of funding not stated. Two study authors declared potentially relevant financial relationships with not-for-profit sources; the remaining author declared no competing interests.**

Self-Report Measure of Negative Symptoms

In a small study, a brief, easy-to-administer self-report scale of negative symptoms in schizophrenia was found to have good psychometric properties and convergent validity with widely used clinician-rated scales.

Background: About 20 screening tools exist to measure negative symptoms of schizophrenia, nearly all of which include 5 symptom dimensions: asociality, blunted affect, avolition, anhedonia, and alogia. No patient-rated scale assessing the accepted 5 domains is believed to exist. Self-assessment of symptoms allows patients to evaluate their own functioning, which could provide clinically important information not necessarily detected by clinician-rated scales.

Methods: The Self-evaluation of Negative Symptoms (SNS) was developed from verbatim reports on negative symptoms by 28 patients during 5 focus groups. The 20 items cover the 5 established negative symptom domains. Each item is scored on a scale of 0 (strongly disagree) to 2 (strongly agree), with higher scores reflecting more severe symptoms, to a maximum total score of 40. A validation study of the SNS was carried out in 23 patients with schizophrenia and 26 with schizoaffective disorder, recruited from a French university psychiatric clinic. All patients were clinically stable and receiving antipsychotic drugs. Exclusion criteria were substance abuse within the past month and mental retardation. Patients completed the SNS at the same time as several other, observer-rated scales commonly used in clinical practice. To measure test-retest reliability, a second SNS was administered 4–8 weeks after the first.

Results: The SNS showed a high level of internal consistency and high test-retest reliability. Construct validity was tested using a factor analysis. Two factors were identified. The first, accounting for 54% of variance, included anhedonia, avolition, asociality, and alogia subscores. The second, consisting of diminished emotional range, accounted for 21% of variance. In addition, significant positive correlations were found between the SNS and the Scale for the Assessment of Negative Symptoms (SANS) total score ($p < 0.0001$), the Clinical Global Impression–Severity negative score ($p < 0.0001$), and the Brief Psychiatric Rating Scale (BPRS) negative scale ($p = 0.037$). Three of the SNS subscales correlated with their corresponding subscales on other instruments. Diminished emotional range and anhedonia were not correlated with SANS blunted affect or anhedonia/asociality. Also, SNS scores were not correlated with measurements of insight, parkinsonism, or BPRS positive symptoms.

Discussion: The SNS is straightforward, and patients can complete it without help. Results of this validation study indicate patients with schizophrenia can complete the measure reliably and consistently. Due to its short format and limited response options, the SNS is well adapted to patients with impaired concentration or cognitive deficits.

Dolifus S, Mach C, Morello R: Self-Evaluation of Negative Symptoms: a novel tool to assess negative symptoms. *Schizophrenia Bulletin* 2016;42 (May):571-578. From the Centre Hospitalier Universitaire de Caen, France. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

Reference Guide

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.

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PSYCHIATRY ALERTS NOS

ADHD: Adult-Onset.....	40
ADHD: Persistent vs. New-Onset	40
Behavioral Activation Therapy.....	37
Brain Stimulation for Generalized Anxiety.....	39
Gratitude Writing and Mental Health.....	41
Mindfulness Therapy in Depression	38
Reference Guide	42

Volume VIII / July 2016 / Number 7

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New CME Activities Coming Soon . . . Have You Enrolled?

Behavioral Activation Therapy for Bipolar Depression

In a pilot study, behavioral activation (BA) therapy modified to accommodate heightened reward sensitivity was feasible and effective in patients with bipolar depression.

Methods: Study subjects were 12 adults with DSM-IV-TR bipolar I or II disorder. Participants were required to be experiencing a current depressive episode, to be receiving stable medication, and to be supervised by a community provider. BA therapy comprised 16 individual sessions, attended weekly for the first 12 weeks and biweekly thereafter, with 4 optional booster sessions. Therapy was based on a manual for treating unipolar depression, but it was modified to address heightened goal striving, which is common in bipolar disorder and can result in overly stimulating or ambitious plans for behavior change. Patients monitored their mood closely throughout the day to identify prodromal manic symptoms. The intervention also included safety planning and monitoring for suicidal behavior. Treatment efficacy was measured using the Inventory of Depressive Symptomatology–Clinician Rating (IDS-C), the mania subscale of the Clinician-Administered Rating Scale for Mania (CARS-M), and the Modified Scale for Suicidal Ideation.

Results: Most patients (n=10) completed treatment, 1 stopped after 3 sessions and was lost to follow-up, and 1 was rehospitalized after 4 sessions. Including these 2 patients, average attendance was 15 of the 16 sessions. All participants had type I bipolar disorder. Depression was generally severe at baseline, and patients were receiving an average of 3 psychotropic medications (with 7 patients receiving an antidepressant).

After completing BA therapy, patients showed significant improvement in IDS-C scores ($p=0.001$; effect size, * 1.3). A total of 6 patients met criteria for response, defined as a $\geq 50\%$ reduction from baseline in symptom severity. The majority of patients (n=10) met a statistical threshold for clinically significant depression improvement. Manic symptom scores on the CARS-M, only mildly elevated at baseline, also improved significantly with BA therapy ($p=0.025$; effect size, 1.0). Baseline scores for suicidal ideation were in the moderate range and also improved significantly with treatment ($p=0.005$; effect size, 1.0).

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Participants gave their therapy a mean rating of 30.5 on the 8-item Client Satisfaction Questionnaire, which has a maximum approval score of 32. Many identified specific areas in which the treatment was helpful, such as education, functional analysis of behavior, alternatives to mood-dependent behavior, and behavioral exercises.

Discussion: Outcomes of BA therapy in this study, although preliminary, are comparable to those observed in unipolar depression. BA may also be promising as a nonpharmacologic approach to suicide risk reduction. The improvement in manic symptoms may reflect improvement in symptoms common to mania and depression, such as irritability and agitation; this finding also argues for the safety of BA therapy in bipolar disorder. However, patients remained symptomatic after completing therapy, which suggests a longer treatment duration may have better results.

Weinstock L, Melvin C, Munroe M, Miller I: Adjunctive behavioral activation for the treatment of bipolar depression: a proof of concept trial. *Journal of Psychiatric Practice* 2016;22 (March):149–158. From Brown University and Butler Hospital, Providence, RI; and Miami University of Ohio, Oxford. **Funded by the NIMH. The authors declared no competing interests.**

*See Reference Guide.

Mindfulness Therapy for Depression Relapse Prevention

An individual patient data meta-analysis* found that mindfulness-based cognitive therapy (MBCT) reduces depressive relapses in high-risk patients for more than 1 year, compared with treatment as usual or with maintenance antidepressant medication, the current mainstay approach.

Methods: A comprehensive literature search identified all randomized clinical trials comparing manual-based MBCT with active or inactive control conditions in adults with recurrent major depressive disorder, currently in full or partial remission according to a formal diagnostic classification. MBCT was compared with treatment as usual in 5 studies and with maintenance antidepressants in 4; 1 study had an additional treatment arm—cognitive psychological education. Patient-level data from the 9 identified trials (n=1258; mean age, 47 years) were pooled to evaluate depression relapse, defined as fulfilling diagnostic criteria for a new major depressive episode, over 60 weeks of follow-up.

Results: MBCT was associated with reduced risk of depression relapse compared with all control conditions (hazard ratio,* 0.69) and all active comparator treatments (hazard ratio, 0.79). The efficacy of MBCT was not influenced by patient age; gender; relationship status; race/ethnicity; education; socioeconomic status; or employment status. Mindfulness at baseline also did not moderate the efficacy of MBCT. Of a variety of illness-related characteristics, efficacy was only predicted by a greater severity of depressive symptoms at baseline. In studies that reported adverse events, none were attributed to MBCT.

Discussion: These results support the efficacy of MBCT for relapse prevention and suggest that its effects may be generalizable to a wide patient population. It appears that MBCT could be particularly helpful to patients who still have significant depressive symptoms after acute treatment.

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

Kuyken W, Warren F, Taylor R, Whalley B, et al: Efficacy of mindfulness-based cognitive therapy in prevention of depressive relapse: an individual patient data meta-analysis from randomized trials. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.0076. From Warneford Hospital, University of Oxford, U.K.; and other institutions. **Funded by the Wellcome Trust; and other sources. Six study authors disclosed potentially relevant financial relationships; the remaining 12 authors declared no competing interests. See related story in *Psychiatry Alerts NOS* 2015;7 (May):25–26.**

*See Reference Guide.

Brain Stimulation for GAD

In a pilot study, repetitive transcranial magnetic stimulation (rTMS) improved symptoms of generalized anxiety disorder in a group of adults with at least moderate symptoms.

Background: Following the observation that patients receiving FDA-approved rTMS for depression also experienced improvement in anxiety, this small randomized controlled trial investigated rTMS delivered to the right dorsolateral prefrontal cortex (DLPFC), an alternative target sometimes used in depression treatment.

Methods: Study subjects were adults (n=25; 19 women) with a confirmed diagnosis of GAD who met minimum criteria for symptom severity (i.e., Hamilton Anxiety Rating Scale [HAM-A] score of ≥ 18 and a Clinical Global Impression–Severity scale rating of at least moderately ill). Participants were randomly assigned to double-blind treatment with either active (n=13) or sham (n=12) rTMS. Active treatment consisted of rTMS at 1 Hz for 15 minutes at 90% of the resting motor threshold, 5 days a week for 6 weeks. Sham treatment followed the same protocol but used a sham coil that delivered subthreshold stimulation. The primary efficacy measure was the HAM-A, assessed immediately post-treatment and at 3-month follow-up. Before and after treatment, patients underwent functional MRI brain scans while completing a decision-making task designed to cause stressful uncertainty.

Results: Following acute treatment, both groups experienced large, statistically significant reductions from baseline in anxiety symptoms ($p < 0.001$; see table), but active rTMS was associated with persistent benefits ($p < 0.001$) at 3-month follow-up while sham treatment was not. Changes in the secondary study outcome measures of self-rated worry and depression and clinician-rated depression also showed medium-to-large effect sizes* that persisted at the 3-month follow-up. Rates of response ($\geq 50\%$ decrease in HAM-A score) were significantly higher with active treatment at both end of treatment (78% vs. 20%; $p = 0.01$) and at 3-month follow-up (78% vs. 0%; $p = 0.001$). Remission (HAM-A score < 8 and a CGI-Improvement rating of very much or much improved) was also more frequent with active treatment, but the between-group difference was significant only at 3-month follow-up (68% vs. 0%; $p = 0.003$).

HAM-A Changes from Baseline to Follow-Up					
	Baseline	Post-Treatment	Effect Size	Follow-Up	Effect Size
Active rTMS	25.3	12.1	1.91	10.3	1.6
Sham rTMS	20.8	14.4	1.47	18.0	0.4

Functional MRI studies showed that activation of the right DLPFC increased after active treatment and tended to decrease after sham treatment. Changes in the right DLPFC were significantly correlated with changes in worry symptoms ($p = 0.02$) and tended to correlate with changes in anxiety symptoms ($p = 0.06$), with activation increasing as symptoms improved.

Common adverse effects of both active and sham rTMS included pin prick sensation (69% vs. 83%, respectively); stimulation site pain (85% vs. 67%); and facial pain (23% vs. 8%). Only facial twitching occurred significantly more often with active treatment (46% vs. 0%; $p < 0.01$). Of the 25 patients enrolled, 19 completed treatment—9 in the active treatment group and 10 in the sham group.

Discussion: The optimal parameters of rTMS for GAD are unknown. The treatment schedule in this study was burdensome, leading to refusal or withdrawal by many patients. The optimal anatomic target of rTMS in anxiety is also unknown. In the present study, stimulation

was applied to the DLPFC because of its role in emotion regulation. Increased activation in this area may represent normalization of prior DLPFC hypoactivation, leading to better top-down control of emotional processes.

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

Diefenbach G, Bragdon L, Zertuche L, Hyatt C, et al: Repetitive transcranial magnetic stimulation for generalised anxiety disorder: a pilot randomised, double-blind, sham-controlled trial. *British Journal of Psychiatry* 2016; doi 10.1192/bjp.bp.115.168203. From The Institute for Living, Hartford; and Yale University, New Haven, CT. **Funded by the Hartford HealthCare Research Funding initiative. Three study authors disclosed financial relationships with commercial sources; the remaining 8 authors declared no competing interests.**

*See Reference Guide.

Persistent vs. New-Onset ADHD in Early Adulthood

Results of a longitudinal study of children in the U.K. suggest that a significant proportion of ADHD in young adulthood is of recent onset and differs clinically from childhood-onset ADHD that persisted into young adulthood.¹

Methods: The study sample comprised a representative cohort of identical and fraternal same-sex twin pairs born in England and Wales in 1994 or 1995. Families were enrolled when the children were aged 5 years, and follow-up assessments were conducted at ages 7, 10, 12, and 18 years. Presence of childhood ADHD was based on reports by mothers and teachers of symptoms from the DSM-IV diagnostic criteria and the Rutter Child Scales. In young adults, ADHD diagnosis was based on DSM-5 criteria; patients were required to have ≥ 5 inattentive and/or ≥ 5 hyperactivity-impulsivity symptoms, and the symptoms had to be impairing and pervasive.

Results: A total of 2040 participants were assessed both during childhood and at age 18 years. Of these, 12% met criteria for ADHD during childhood, but the disorder persisted into adulthood in only 22% of these patients (3% of the entire cohort). At age 18 years, 8% of the cohort met criteria for ADHD; onset was new in 68%.

Compared with patients with persistent ADHD, those with late-onset were more likely to be women (odds ratio [OR],* 2.48) and had fewer childhood externalizing problems (OR, 0.93) and higher IQ (OR, 1.04). Prenatal, perinatal, and childhood environmental factors were not associated with late-onset ADHD. Young adults with persistent ADHD had higher rates of generalized anxiety disorder (OR, 5.19), conduct disorder (OR, 2.03), and marijuana dependence (OR, 2.88) than those whose ADHD had remitted, but even those who achieved remission had high rates of various types of impairment.

Discussion: An accompanying editorial suggests a potential explanation for the current findings: Subthreshold ADHD may elude diagnosis during childhood but decompensate in early adulthood, perhaps due to greater intellectual challenges and the loss of a supportive family environment.²

¹Agnew-Blais J, Polanczyk G, Danese A, Wertz J, et al: Evaluation of the persistence, remission, and emergence of attention-deficit/hyperactivity disorder in young adulthood. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.0465. From King's College London, U.K.; and other institutions. **Funded by the United Kingdom Medical Research Council. The authors declared no competing interests.**

²Faraone S, Biederman J: Can attention-deficit/hyperactivity disorder onset occur in adulthood [editorial]? *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.0400. From SUNY Upstate Medical University, Syracuse, NY; and other institutions. **Both authors disclosed potentially relevant financial relationships.**

*See Reference Guide.

Adult-Onset ADHD

Evidence from a Brazilian birth-cohort study suggests that a significant proportion of ADHD observed in young adults may be of recent onset.¹ This finding contradicts the DSM-5 diagnostic criterion of symptom onset before age 12 years.

Methods: Participants in this ongoing study were enrolled at birth and represent all children born in a single Brazilian city in 1993 (n=5249). They were assessed at age 11 years with the Strengths and Difficulties Questionnaire (SDQ), which can predict a diagnosis of ADHD with about 80% accuracy. ADHD was defined as present if a child met the investigators' hyperactivity-symptom threshold on the SDQ and had related impairment. At the ages of 18–19 years, participants were interviewed by psychologists using structured instruments for different psychiatric disorders. At this time point, ADHD diagnosis was made according to DSM-5 criteria, omitting the age criterion. To minimize bias from comorbid disorders that might contribute to ADHD symptoms, separate analyses were conducted with the entire young adult-onset ADHD cohort and excluding those with comorbid disorders.

Results: ADHD was present in 393 of >4400 children screened at age 11 years (9%). In the young adult sample (aged 18–19 years; n=4032), 492 participants (12%) met all of the DSM-5 criteria for ADHD except age at onset. After excluding young adults with comorbid disorders, 6.3% had ADHD with onset after their 12th birthday.

Of children with ADHD, 15% continued to have ADHD as young adults, 73% were free of ADHD, and the remaining 12% were lost to follow-up, resulting in a persistence rate of 17%. Of the young adults with ADHD, 12% had childhood-onset ADHD, 85% did not, and the rest were not assessed. Restricting the analysis to individuals with no comorbidity did not change the general findings.

Childhood-onset ADHD occurred predominantly in males (64%), while only 39% of the young adult ADHD cohort was male. Inattentive symptoms predominated in young adults with ADHD, including those with childhood onset. Rates of comorbid major depressive disorder; bipolar disorder; generalized anxiety disorder; social anxiety disorder; illicit drug use; and tobacco smoking were all elevated in young adults with both childhood-onset and young adult-onset ADHD. Compared with their ADHD-free peers, self-reported suicide attempts in young adulthood were more frequent in those with childhood-onset ADHD (10% vs. 6%; $p=0.003$) and in those with young adult-onset ADHD (15% vs. 5%; $p<0.001$). In young adults, ADHD was also associated with higher rates of incarceration, teenage pregnancies, sexually-transmitted diseases, and traffic incidents.

Discussion: Although these findings replicate those of a previous longitudinal study,² they do not support the generally accepted notion that adult-onset ADHD is necessarily a continuation of childhood ADHD. Rather, they suggest the existence of 2 syndromes (childhood- and late-onset ADHD) that have distinct developmental trajectories but similar types of impairment.

¹Caye A, Rocha T, Anselmi L, Murray J, et al: Attention-deficit/hyperactivity disorder trajectories from childhood to young adulthood: evidence from a birth cohort supporting a late-onset syndrome. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.0383. From the Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; and other institutions. **Funded by the Brazilian National Council for Scientific and Technological Development; and other sources. Four study authors disclosed financial relationships with commercial sources; the remaining 9 authors declared no competing interests.**

²Moffitt T, et al. Is adult ADHD a childhood-onset neurodevelopmental disorder? Evidence from a four-decade longitudinal cohort study. *American Journal of Psychiatry* 2015;172(10):967–977.

Adjunctive Gratitude Writing Improves Mental Health

In a randomized controlled trial, adjunctive gratitude writing enhanced the positive effects of psychotherapy in treatment-seeking patients.

Methods: Study participants were 293 adults (mean age, 22 years) seeking individual psychotherapy at a university counseling center or a community-based training clinic. Participants were required to be new patients with clinical levels of distress based on General Mental Health (GMH) Index of the Behavioral Health Measure-20 scores, and to be willing to commit to

≥3 weekly psychotherapy sessions. Subjects were randomly assigned to adjunctive gratitude writing, expressive writing, or no adjunctive assignments. Gratitude writing consisted of 3 weekly homework assignments in which the patient wrote a letter expressing gratitude to a person they had not previously thanked properly. Letters could be to the same person or different people, and the patient had the choice of whether or not to send the letters. The control intervention, expressive writing, consisted of 3 assignments in which the patient was instructed to write about their most stressful and upsetting experiences. Participants were told their therapist would not be informed of their participation in the writing study. The primary outcome was the GMH index, which measures well-being, psychological symptoms, and life functioning, assessed 1 week, 4 weeks, and 12 weeks after the last writing session.

Results: Of 127 clients assigned to gratitude writing, 44 did not complete the assignments; 21 of the 91 assigned to expressive writing did not participate. The intent-to-treat analysis, which included all randomized participants, showed that all treatments were associated with improvement, with an effect size* of 0.98 from baseline to last follow-up. Outcomes in the expressive writing and no-treatment groups did not differ and they were combined for further analysis. Participants in the gratitude exercise showed larger improvements in GMH index score than controls. The between-group differences were statistically significant 4 and 12 weeks after the last writing assignment was completed ($p < 0.03$).

Discussion: Based on these preliminary results, selective clinical use of gratitude letter writing in clients who would find it meaningful appears to be warranted. Benefits could be enhanced if therapists discuss insights gained from writing.

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

Wong Y, Owen J, Gabana N, Brown J, et al: Does gratitude writing improve the mental health of psychotherapy clients? Evidence from a randomized controlled trial. *Psychotherapy Research* 2016; doi 10.1080/10503307.2016.1169332. From Indiana University, Bloomington; and other institutions. **Funded by the John Templeton Foundation. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Reference Guide

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.

Individual Patient Data Meta-Analysis: A specific type of systematic review in which original patient-level research data are sought directly from the researchers responsible for each study, rather than extracting summary data from study publications.

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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PSYCHIATRY ALERTS NOS

Blue Light and Manic Symptoms	45
Brain Stimulation for Alcohol Dependence.....	46
Complicated Grief Treatment	47
Nutraceuticals for Depression.....	43
Reference Guide	48
Trauma-Focused Treatment in Psychosis	44

Volume VIII / August 2016 / Number 8

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New CME Activities Have Been Released . . . Have You Enrolled?

Adjunctive Nutraceuticals for Depression

Despite limited evidence, some nutraceuticals can be recommended as adjunctive treatments for depression, according to a systematic review and meta-analysis. Positive effects were found for SAME, omega-3 fatty acids, vitamin D, and, tentatively, methylfolate and folinic acid.

Methods: A comprehensive literature search identified all published literature for evidence regarding 14 different nutraceuticals (i.e. standardized pharmaceutical-grade nutrients) used to augment pharmaceutical antidepressants that have biological effects known to be related to brain function. The analysis included uncontrolled, controlled, and quasi-experimental studies in patients with a diagnosis of major depression, either primary or comorbid, or who had ongoing moderate or above-threshold depressive symptoms. Primary treatment with an antidepressant was required. Studies were required to have >10 subjects per treatment arm, to provide treatment for ≥ 21 days, and to report the outcome using a recognized depression scale. Results were tabulated separately for 4 categories of nutraceutical: one-carbon cycle, omega-3, tryptophan, and others.

Results: A total of 40 studies, including 31 randomized placebo-controlled trials, met the inclusion criteria. Common trial lengths were 4, 6, and 8 weeks (range, 3–52 weeks), and the average sample size was 63 (range, 20–475).

A total of 15 data sets in 14 studies examined one-carbon cycle nutraceuticals: SAME (4 studies), folic acid monotherapy (5 studies), or other nutrients or combinations. Of these, 10 found a positive effect, either in comparison to placebo or beyond baseline in nonresponsive depression. When different agents were analyzed separately, however, effects were primarily positive for SAME and mixed or nonsignificant for the other nutrients. A meta-analysis of the 4 folic acid studies found no significant effect. Methylfolate or folinic acid were efficacious in 2 small trials and 1 substudy of a larger trial, but the largest study—a placebo-controlled trial of methylfolate in 148 patients with SSRI-refractory depression—found no effect.

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Eight studies evaluated the effects of omega-3 fatty acids. A meta-analysis combining all studies showed an effect that was statistically significant ($p=0.009$) but modest (effect size,* 0.61). The effect was strengthened, but only slightly, when the analysis was limited to EPA-only omega-3 formulations.

Tryptophan was investigated in 8 studies. Of these, 7 were published before 1985, and at that time, tryptophan was added to older classes of antidepressants (e.g., tricyclics or MAOIs). Five studies showed a positive effect. A meta-analysis of these studies could not be conducted because data were unavailable from many of the early studies.

Other nutrients were rarely studied, but positive effects were found for vitamin D (2 studies), creatine (1 study), and an amino acid combination (1 study). There were mixed effects for zinc and vitamin C (2 studies each) and no benefit for inositol.

All of the nutraceuticals were very well tolerated, with <2% of patients discontinuing due to adverse effects in any study. However, it should be noted that nutraceuticals are not without risk, particularly when used at high doses and over extended periods, and when combined with certain medications.

Sarris J, Murphy J, Mischoulon D, Papakostas G, et al: Adjunctive nutraceuticals for depression: a systematic review and meta-analysis. *American Journal of Psychiatry* 2016;173 (June):575–587. From the University of Melbourne, Australia; and other institutions. **Funded by the University of Melbourne; the National Health and Medical Research Council; and other sources. Six study authors disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

*See Reference Guide.

Trauma-Focused Treatment in PTSD with Psychosis

In patients with psychosis, comorbid PTSD is usually not diagnosed, and treatment is not offered out of fear of destabilizing the patient and causing suicide, revictimization, and other adverse events. According to a secondary analysis of a randomized controlled trial, trauma-focused therapy for PTSD is safe and associated with a low risk of adverse effects in patients with psychosis. Treatment also appears to be highly effective in preventing revictimization.

Methods: The randomized trial compared 2 PTSD treatments—prolonged exposure therapy and eye movement desensitization and reprocessing therapy—with a wait-list control. The 2 active treatments were equally effective and superior to the control; in the present analysis, the treatments were combined. Participants were patients from 13 Dutch outpatient services treating severe mental illness. The majority of the 155 patients (mean age, 41 years; 46% men) had schizophrenia (61%) or schizoaffective disorder (29%). Patients had high rates of delusions (62%) and hallucinations (40%) and a medium-to-high suicide risk. All patients received usual care for their psychotic disorder. In addition, the trauma-focused treatments were given in 8 sessions over 10-weeks. Symptoms were assessed at baseline, end of treatment, and 6 months post-randomization with standardized clinician- and patient-rated inventories. Patients were asked whether they had experienced adverse events such as suicide attempts; self-harm; substance abuse; use of crisis services; and psychiatric hospitalization. Revictimization was assessed by self-report.

Results: Significantly fewer participants receiving active treatment than those on the wait list experienced a PTSD symptom exacerbation, as evidenced by a worsening score on either the Clinician-Administered PTSD Scale or the Posttraumatic Stress Symptom Scale Self-Report score during treatment (14% vs. 31%; $p=0.05$). Compared with wait-listed controls, patients receiving trauma-focused therapy also had lower rates of paranoid ideation and fewer symptoms of depression, although differences were mostly small and not statistically significant.

Following the first active trauma-focused session, 87% of patients had stable symptoms and 12% showed an improvement. Both paranoid ideation and suicidality decreased significantly beginning after the first treatment session, and paranoid ideation and dissociative feelings decreased with the second session.

Patients who received trauma-focused therapy were as also significantly less likely to experience a psychological adverse event than wait-list controls (odds ratio,* 0.48; $p=0.03$). About 2% of each group made a suicide attempt. Revictimization occurred at equal rates during treatment but was markedly less frequent in the active-treatment groups during the months following the end of treatment (odds ratio, 0.16; $p=0.003$).

van den Berg D, de Bont P, van der Vleugel B, de Roos C, et al: Trauma-focused treatment in PTSD patients with psychosis: symptom exacerbation, adverse events, and revictimization. *Schizophrenia Bulletin* 2016;42 (May):693–702. From the Parnassia Psychiatric Institute, the Hague, the Netherlands; and other institutions. **Funded by the Dutch Support Foundation "Stichting tot Steun VCVGZ."** Five study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.

*See Reference Guide.

Blue Light and Manic Symptoms

In a randomized controlled trial, preventing blue light from entering the retina reduced mania symptoms when added to usual therapy.

Background: Blue light can be blocked by wearing orange-tinted glasses. These glasses block stimulation of the intrinsically photo-responsive retinal ganglion cells (ipRGCs), which directly signal the light/dark status of the environment and also interact indirectly with several brain regions. Blocking blue light by wearing orange glasses has been shown to create a state of virtual darkness in the brain while preserving the normal nighttime melatonin profile.

Methods: Study participants were inpatients with bipolar mania recruited from 5 hospitals in Norway and healthy controls living in the same locales. Previous knowledge of blue-blocking (BB) glasses was grounds for exclusion of patients, but not controls. By random assignment, patients wore BB glasses or clear-lensed placebo glasses while awake between 6 PM and 8 AM for 7 days. Treatment could not be masked, but patients were told that they were testing different types of glasses that blocked different light wavelengths. All patients continued to receive background treatment as usual. Patients' manic symptoms were scored daily using the Young Mania Rating Scale (YMRS), the primary outcome measure. Activity was monitored using a wrist-worn actigraph. Controls were monitored for a 7-day baseline followed by 7 days wearing the BB glasses.

Results: A total of 32 patients were randomized, but 8 withdrew consent on the first night or were unable to adhere to the protocol, leaving 13 patients in the BB-glasses group and 11 in the placebo group. Actigraph recordings were analyzed for 12 patients wearing BB glasses, 10 wearing clear glasses, and 35 healthy controls.

Patients who wore BB glasses had a larger improvement in the YMRS total score than the placebo group, reaching statistical significance at day 3 ($p=0.04$) and continuing to diverge by day 7 ($p=0.001$). The mean reduction from baseline in the YMRS was 14 points with BB glasses, compared with 2 points with placebo glasses (effect size,* 1.86). Two of the 11 YMRS items—Irritability and Language-Thought Disorder—improved immediately in patients wearing BB glasses, while several other individual YMRS items showed more gradual improvement. Patients wearing BB glasses received fewer pharmacological agents during the treatment week than the placebo group. Also, 2 patients were transferred out of acute wards because of striking improvement.

Actigraphy showed lower movement between 6 PM and 8 AM in the BB-glasses group compared with the placebo group and a marked decline in activity between the first and second night of wearing BB glasses ($p=0.018$), a pattern not observed in healthy controls.

Patients generally reported that the BB glasses were tolerable. Two patients experienced emerging depressive symptoms, but these were controlled by delaying the start of wearing the glasses or by skipping a day. Headache developed while wearing BB glasses in 1 patient with a history of migraine and in 3 healthy controls. Several of the healthy control patients experienced transient lowered mood or energy.

Discussion: Despite the small sample size, in part due to enrollment difficulties as more of the general population became aware of BB glasses, this study was sufficient to test the hypothesis that BB glasses are a useful adjunctive anti-manic treatment. The rapid reduction of some manic symptoms suggests that the effects of the glasses may occur via silencing of signalling in the ipRGC circuits that directly influence mood and cognition, rather than indirect effects on melatonin, sleep, or increased circadian synchrony, although these mechanisms may also produce delayed effects on mania.

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

Henriksen T, Skrede S, Fasmer O, Schoeyen H, et al: Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial. *Bipolar Disorders* 2016;18 (May):221–232. From the University of Bergen, Norway; and other institutions. **Funded by Fonna Local Health Authority; and other sources. The authors declared no competing interests.**

*See Reference Guide.

DBS for Alcohol Dependence

In a small series of patients with severe alcohol addiction, deep brain stimulation of the nucleus accumbens eliminated alcohol cravings. The treatment had mixed results in controlling drinking over long-term follow-up.

Background: Previous publication of the first 3 cases in this series attracted considerable controversy over the ethics of using brain stimulation for "behavioral" disorders. Since then, other researchers have studied DBS in heroin and cocaine addiction. The experimental treatment is based on the hypothesis that DBS may normalize or "free" the reward system of the brain, which has been "hijacked" by alcohol. Thus, craving may be eliminated, but other reasons for drinking (e.g., negative reinforcement) may persist, and alcohol-related neurotoxicity can lead to lasting damage of brain tissue.

Methods: DBS was undertaken in 5 men, aged 25–60 years, with a ≥ 10 -year history of alcohol dependence, failure of ≥ 2 rehab treatments totaling ≥ 6 months, and failure of treatment with acamprosate, naltrexone, or disulfiram. Patients first underwent inpatient detoxification, followed by a 2-week period of abstinence prior to surgical implantation of bilateral DBS devices. All patients received continuous care, including psychiatric outpatient care, covered by their national health insurance.

Results: Of the 3 initial patients, 1 remained abstinent at 8 years. The second remained abstinent at last contact (6 years after starting DBS), after which he was lost to follow-up. The third patient had multiple drinking relapses over 8 years of follow-up before he died in 2015. He had reported that he would have been worse without DBS. The fourth patient also died (4 years after starting DBS). He continued to relapse with treatment but also claimed he would drink more without it. He blamed his relapses on stress, not craving. The final patient continues to have brief relapses every few months to relieve stress, adding up to about 50 drinking days per year, which he says would have been impossible for him previously. Scores on the Alcohol

Urge Questionnaire varied pretreatment but dropped to normal levels with DBS in all 5 patients who also reported an absence of cue-related craving, such as when walking past a bar. No definite cause of death was recorded for either patient who died, but alcohol was suspected in both cases. In both cases, there was no autopsy evidence of complications of DBS.

All patients reported very positive experience with DBS; they described an overall health benefit and did not describe adverse effects or negative consequences. DBS did not suppress the reward system or lead to a lack of pleasurable feelings.

Muller U, Sturm V, Voges J, Heinze H, et al: Nucleus accumbens deep brain stimulation for alcohol addiction—safety and clinical long-term results of a pilot trial. *Pharmacopsychiatry* 2016; doi 10.1055/s-0042-104507. From Otto-von-Guericke-University of Magdeburg; and the University of Cologne, Germany. **Source of funding not stated. The authors declared no competing interests.**

Common Drug Trade Names: acamprosate—*Campral*; disulfiram—*Antabuse*; naltrexone—*ReVia*

Treatment of Complicated Grief

Complicated grief treatment (CGT), a manualized 16-session psychotherapy program, was superior to citalopram (*Celexa*) in treating complicated grief in a randomized trial.¹ Combined treatment provided additional benefit only in co-occurring depression.

Background: The authors of this study developed CGT and previously found that it produced greater benefit than grief-focused interpersonal psychotherapy.² Sessions in the CGT protocol include, in order of occurrence: history taking; introduction of daily grief monitoring and ongoing aspirational goals work; imaginal and situational revisiting procedures; work with memories and pictures; and imaginal conversations with the deceased. The treatment manual is available at <https://complicatedgrief.columbia.edu/>.

Methods: Study participants were 395 adults, aged ≤95 years, who had minimum screening scores on the Inventory of Complicated Grief and completed a confirmatory clinical interview. Subjects were randomized to receive citalopram monotherapy (n=101), placebo monotherapy (n=99), citalopram plus CGT (n=99), or placebo plus CGT (n=96). Medication was flexibly dosed, and all participants met regularly with a pharmacotherapist who provided emotional support in addition to medication management and symptom monitoring. The primary efficacy outcome was response, defined as a complicated grief-specific Clinical Global Impression–Improvement rating of "much improved" or "very much improved."

Results: Rates of response were higher in patients who received CGT than in those who did not. (See table.) Contrary to the authors' expectations, the addition of citalopram to CGT did not improve the response rates. Also unexpectedly, response rates with citalopram were numerically, but not statistically, greater than with placebo.

Response Rate Comparisons at Week 12				
	Response rates	Relative risk* of response	Significance	Number needed to treat*
CGT alone vs. placebo monotherapy	83% vs. 55%	1.51	p=0.002	3.6
CGT plus citalopram vs. CGT alone	84% vs. 83%	1.01	p=ns	84
Citalopram monotherapy vs. citalopram plus CGT	69% vs. 84%	1.21	p=0.05	6.9
Citalopram monotherapy vs. placebo monotherapy	46% vs. 38%	1.21	p=ns	12.4

In patients with major depressive disorder, grief did not respond to citalopram to a greater degree than in patients without depression. However, depressive symptoms decreased more with CGT in patients who also received citalopram. CGT was associated with significantly lower rates of suicidal ideation at week 20, compared with citalopram alone.

Six-month follow-up data, available for 63% of patients, showed that responses were maintained in >93% of all groups except the placebo group.

Discussion: The study authors recommend CGT as first-line treatment for complicated grief. Antidepressants may be used for relief of co-occurring depressive symptoms. The robust placebo response suggests that pharmacotherapist interaction had a substantial therapeutic effect. The study authors recommend providing CGT-informed support if the therapy itself is not available.

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

¹Shear M, Reynolds C III, Simon N, Zisook S, et al: Optimizing treatment of complicated grief: a randomized clinical trial. *JAMA Psychiatry* 2015; doi 10.1001/jamapsychiatry.2016.0892. From Columbia University, New York, NY; and other institutions. **Funded by the NIMH; and the American Foundation for Suicide Prevention. Three study authors disclosed financial relationships with commercial sources; the remaining 6 authors declared no competing interests.**

²Shear M, et al: Treatment of complicated grief in elderly persons: a randomized clinical trial. *JAMA Psychiatry*. 2014;71(11):1287–1295. See *Psychiatry Alerts NOS* 2014;6 (October):57–58.

*See Reference Guide.

Reference Guide

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.

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

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PSYCHIATRY ALERTS NOS

Brain Stimulation for Binge Eating	49
Depression Guidelines: Psychological Therapy	53
ECT in Geriatric Depression	51
Glutamate in Schizophrenia.....	50
Reference Guide	54
Social Anxiety Disorder: Online Treatment	52

Volume VIII / September 2016 / Number 9

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New CME Activities Have Been Released . . . Have You Enrolled?

tDCS in Binge Eating Disorder

A single session of transcranial direct current brain stimulation reduced craving and enhanced control of food intake in research subjects with binge eating behavior. Results of this proof-of-concept study suggest repeated tDCS may have potential as an adjunct to the behavior therapies that are currently standard treatment for binge eating disorder (BED).

Background: First-line treatment of BED consists of cognitive behavioral therapy or dialectical behavior therapy. Adjunctive repetitive transcranial magnetic stimulation (rTMS) has shown promise in treating eating disorders, but tDCS is safer, less expensive, and easier to administer.

Methods: The study enrolled 30 subjects who either met diagnostic criteria for BED or had subthreshold symptoms, meeting all criteria except the minimum frequency of episodes. No participants were receiving treatment for BED. Subjects were assessed at baseline with questionnaires to elicit eating motivation and intention to restrict eating, and then they received treatment once with real and once with sham tDCS in random sequence. tDCS consisted of 20 minutes of stimulation with the anode placed over the right dorsolateral prefrontal cortex (DLPFC) and the cathode over the left DLPFC. Immediately before and after tDCS, participants completed a food craving test in which they rated 24 different foods—desserts, non-sweet carbohydrates, and savory protein foods—according to "liking" and "wanting." Afterward, in the guise of a "taste test," they were left alone for 20 minutes with different salty or sweet snack foods and asked to rate taste attributes of the foods and discard what they did not eat. After returning home, participants completed a brief electronic survey daily for 5 days, describing binge eating desire and behavior and taste perception.

Results: The mean body mass index of the sample was 36. The 19 participants with BED had an average of about 3 episodes per week, and the 11 with subthreshold symptoms binged about 3 times per month.

tDCS was associated with reductions in self-reported craving for all foods ($p=0.02$) and for desserts ($p=0.02$) and savory proteins ($p=0.01$). A reduction in craving for carbohydrates was

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not statistically significant. In men, tDCS was associated with large reductions in cravings overall and for specific types of foods; reductions in women were smaller and nonsignificant. Active tDCS was associated with an 11% reduction in calories consumed during the "taste test." The post-test assessments showed that tDCS reduced desire to binge-eat for 5–6 hours on the day of treatment, but only in men.

The effects of tDCS on food intake were larger in subjects who had a greater intent to restrict eating at baseline. Of 4 different possible non-hunger motives for eating, tDCS was associated with reductions in eating for reward enhancement. There was no correlation between the effects of tDCS on craving and its effects on food intake.

Discussion: In patients with BED, treatment with tDCS may work by decreasing motivation for reward from palatable foods and reinforcing patients' intention to restrict eating. Lasting effects may be conferred with repeated treatments and subsequent neuroplasticity, but this requires further study.

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

Burgess E, Sylvester M, Morse K, Amthor F, et al: Effects of transcranial direct current stimulation (tDCS) on binge-eating disorder. *International Journal of Eating Disorders* 2016; doi 10.1002/eat.22554. From the University of Alabama at Birmingham. **Funded by a University grant. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Glutamate Alterations in Schizophrenia

Schizophrenia is associated with elevations in glutamatergic metabolites in several brain regions, according to a meta-analysis of proton magnetic resonance spectroscopy (MRS) studies.¹ This finding suggests drugs that reduce glutamatergic neurotransmission may have therapeutic potential in the disorder.

Methods: The meta-analysis included studies published through April 2015, in which MRS was used to compare levels of glutamate, its metabolite glutamine, or both substances (Glx) in affected subjects and healthy controls. Separate meta-analyses were conducted for all cases and for 3 clinical groups: persons at high risk of schizophrenia, first-episode patients, and those with chronic schizophrenia. Data concerning 7 different brain regions of interest were analyzed separately, as were glutamate, glutamine, and Glx. (Only MRS studies using a higher field strength were able to discriminate between glutamate and glutamine.) Statistical significance tests were corrected for the large number of multiple comparisons.

Results: A total of 59 studies were identified with an aggregate sample size of 1686 cases and 1451 controls. Of the studies, 14 examined patients at high risk for psychosis, 18 examined patients with first-episode psychosis, and 36 involved patients with chronic schizophrenia.

Elevations in glutamate metabolites in the basal ganglia were observed the most consistently, with increases in glutamate and Glx found in both cases and controls (although not always in high-risk patients). Other statistically significant findings included higher Glx in the medial frontal cortex of high-risk individuals, in the frontal white matter of persons with chronic schizophrenia, and in the medial temporal lobe in all cases and in patients with chronic schizophrenia. Glutamine was elevated in the thalamus in patients with first-episode and chronic schizophrenia. There were no significant increases in glutamate metabolites in the dorsolateral prefrontal cortex or cerebellum. No brain region showed a reduction in glutamate metabolites in any subject group. Associations were not found between glutamate metabolites and patient age, symptom severity, dose of antipsychotic medication, or duration of illness.

Editorial.² Traditional reliance on PET investigations has supported a bias in favor of biogenic amines as central to the pathology of serious mental disorders. Recent advances in MRS imaging have allowed researchers to measure millimolar concentrations of glutamate and GABA in the brain. Results of studies conducted in the past 2 decades suggest glutamic acid and GABA may be as important as biogenic amines, if not dominant, in the pathology of schizophrenia, affective disorders, and other serious illnesses.

Discussion: Although the results of the meta-analysis varied with clinical group and brain region, all of the significant findings involve elevations of glutamate metabolites in both patients with schizophrenia and those at high-risk for the disorder.

Study Rating*—16 (89%): This study met most criteria for a systematic review / meta-analysis, but individual study quality does not appear to have been assessed.

¹Merritt K, Egerton A, Kempton M, Taylor M, et al: Nature of glutamate alterations in schizophrenia: a meta-analysis of proton magnetic resonance spectroscopy studies. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.0442. From Kings College London, U.K. **Funded by the UK Medical Research Council; and other sources. Three study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

²Coyle J, Konopaske G: Glutamatergic dysfunction in schizophrenia evaluated with magnetic resonance spectroscopy [editorial]. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.0575. From Harvard Medical School, Boston, MA; and other institutions. **One author disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

*See Reference Guide.

Unilateral Ultrabrief Pulse ECT in Geriatric Depression

Right unilateral ultrabrief pulse ECT, combined with venlafaxine (*Effexor*), was highly effective as acute treatment of depression in patients aged ≥ 60 years.¹ Additional ECT after remission helped most patients sustain their improvement.²

Methods: The Prolonging Remission in Depressed Elderly study was conducted in 2 phases, each reported separately. Participants were in- or outpatients referred for ECT and received treatment at 8 sites in the U.S. They had to be aged ≥ 60 years and have DSM-IV unipolar major depressive disorder, with a minimum score of 21 on the 24-item Hamilton Rating Scale for Depression (HAM-D).

Phase 1. After washout of previous medications, all patients were started on open-label venlafaxine, titrated to a target daily dosage of 225 mg/day. Within a few days, they began a course of thrice-weekly unilateral ultrabrief pulse right ECT at 6 times the seizure threshold. The stimulus dose could be increased 50% in the absence of improvement by treatment 6 and again by treatment 9. Depressive symptoms were evaluated at each ECT session. The primary outcome of Phase 1 was remission, defined as 2 consecutive HAM-D scores of ≤ 10 , with no increase of >3 points between evaluations.

Phase 2. Patients who achieved remission in phase 1 were randomly assigned to receive open-label continuation venlafaxine plus lithium alone or with ECT. Venlafaxine was continued at the dose that was effective in phase 1. Lithium was started on the day patients were randomized and titrated to target levels between 0.4 and 0.6 mEq/L, lower than the full therapeutic dose for bipolar disorder. The ECT group received 4 treatments in the first month, with further treatments flexibly scheduled based on the patient's HAM-D score. Depressive symptoms, the primary study outcome, were assessed twice a month with the HAM-D.

Results: The 240 patients who began phase 1 had a mean age of 70 years and baseline HAM-D scores in the severe range (mean, 31). A total of 148 patients (62%) experienced remission, 24 patients (10%) were nonremitters, and the remaining 68 patients (28%) dropped out. In the group that experienced remission, the mean HAM-D score was decreased by 25 points

($p < 0.001$) to 6 at the end of acute treatment. Scores also decreased significantly among patients who did not achieve remission and those who dropped out (-12 and -10 points, respectively; $p < 0.001$ for both). Of the patients who remitted, 20% required ≤ 4 sessions to achieve remission, 45% remitted within 2 weeks (≤ 6 treatments), and 26% required ≥ 10 treatments. Global cognitive function remained stable during acute treatment.

A total of 120 patients entered phase 2 and received ≥ 1 post-treatment evaluation. During this phase, one-third of patients in the ECT group received ≥ 1 additional treatment. At the primary 24-week study endpoint, the baseline-adjusted mean HAM-D score was significantly lower in the group receiving medication plus ECT than in the medication-alone group (5.5 vs. 9.4; $p = 0.004$), and significantly more patients receiving ECT had Clinical Global Impression–Severity ratings of "not at all ill" at study end (odds ratio,* 5.2; $p = 0.009$). There were 12 relapses in the medication-only group and 8 in the medication-plus-ECT group. Rescue ECT was rapidly effective in this group. The treatment groups did not differ in cognitive function during treatment, and no serious adverse events were attributable to ECT.

Discussion: These results confirm the efficacy and rapid effects of right unilateral ultrabrief pulse ECT in a geriatric population. Continuing ECT after remission, rather than abruptly stopping, is likely to help sustain mood improvement. Clinicians should be willing to prescribe additional ECT if symptoms reemerge.

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

¹Kellner C, Husain M, Knapp R, McCall W, et al: Right unilateral ultrabrief pulse ECT in geriatric depression: phase 1 of the PRIDE study. *AJP in Advance* 2016; doi 10.1176/appi.ajp.2016.15081101. From the Icahn School of Medicine at Mount Sinai, NY; and other institutions. **Funded by the NIMH. Seven study authors declared potentially relevant financial relationships; the remaining authors declared no competing interests.**

²Kellner C, Husain M, Knapp R, McCall W, et al: A novel strategy for continuation ECT in geriatric depression: phase 2 of the PRIDE study. *AJP in Advance* 2016; doi 10.1176/appi.ajp.2016.16010118. From the Icahn School of Medicine at Mount Sinai, NY; and other institutions. **Funded by the NIMH. Seven study authors declared potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Online Social Anxiety Treatments

In a randomized trial, internet-delivered cognitive behavioral therapy (CBT) for social anxiety disorder (SAD) was equally effective and acceptable whether it was transdiagnostic or disorder-specific and whether it was clinician- or self-guided.

Methods: The present study compared randomly assigned transdiagnostic CBT (designed to simultaneously treat both the principal disorder and comorbid anxiety and depressive disorders by targeting common symptoms and psychological processes) with disorder-specific CBT in patients with a principal diagnosis of social anxiety disorder. The diagnosis-specific Social Confidence Course was developed by this research group, and the transdiagnostic Wellbeing Course was previously shown to be clinically effective in treating symptoms of anxiety and depression. Both programs consisted of 5 lessons delivered online over 8 weeks, homework assignments, detailed case studies, and additional resources. Within these 2 programs, participants were also randomly assigned to clinician guidance, with weekly protocolized telephone or email contact, or self-guidance consisting of monitoring by therapists and optional contact only for technical assistance or clinical crises. Outcomes were evaluated at the end of treatment and after 3, 12, and 24 months. The primary outcome measure the Mini-Social Phobia Inventory (MINI-SPIN), a 3-item inventory of social anxiety symptoms.

Results: The study enrolled and treated 220 participants (mean age, 42 years; 42% men), of whom 65% had previous mental health treatment and 28% were currently taking psychotropic medication. A total of 81–84% of each group completed 4 CBT sessions (considered the full

dose), 64–70% completed all 5 sessions, and 74–80% had a follow-up assessment at 24 months. There were no differences in completion rates among the 4 treatment groups.

All treatment groups showed large improvement in symptoms of SAD and medium-to-large improvement of the comorbid problems. (See table.) Efficacy outcomes for SAD did not differ between transdiagnostic and diagnosis-specific CBT, and comorbid problems improved to a similar extent with transdiagnostic and disorder-specific therapy.

Change from baseline in symptoms of SAD and comorbid disorders, for all treatment groups combined		
Measure	% Change from Baseline	Effect Size*
MINI-SPIN (SAD)	30%	1.01
PHQ-9 (Depression)	39%	1.25
GAD-7 (Anxiety)	36%	0.86
PDSS (Panic disorder)	25%	0.53

PHQ=Patient Health Questionnaire; GAD=Generalized anxiety disorder; PDSS=Panic Disorder Severity Scale

Clinician-guided and self-guided CBT were equally effective, despite a larger therapist time investment in

clinician-guided CBT. Clinicians spent an average of 37 minutes per patient, telephoning and emailing participants in the clinician-guided program. Clinicians made a total of 4 phone calls to self-guided participants and had a total of 23 email exchanges, spending an average of <1 minute per patient. These contacts were focused on responding to mental health crises.

At the end of treatment, about half of patients no longer met diagnostic criteria for SAD. The average number of comorbid diagnoses decreased from about 2 to slightly less than 1. There were large reductions in psychological distress, disability, and neuroticism. The early results of treatment generally persisted or showed further improvement at 24-month follow-up.

Dear B, Staples L, Terides M, Fogliati V, et al: Transdiagnostic versus disorder-specific and clinician-guided versus self-guided internet-delivered treatment for social anxiety disorder and comorbid disorders: a randomized controlled trial. *Journal of Anxiety Disorders* 2016;42 (August):30–44. From Macquarie University, Sydney; and Curtin University, Australia. **Funded by the Australian National Health and Medical Research Council. The study authors declared no financial relationships with commercial sources.**

*See Reference Guide.

Canadian Depression Guideline: Psychological Treatments

The Canadian Network for Mood and Anxiety Treatments (CANMAT) has updated its guidelines for the use of pharmacotherapy, psychological therapies, neurostimulation, and complementary and alternative treatment of unipolar major depression in adults based on meta-analyses and systematic reviews published between 2009 and 2015. Among changes to the psychological-treatments guideline are the elevation of behavioral activation therapy to first-line treatment, endorsement of computer-based and telephone-delivered therapy, and a discussion of evidence-based therapist factors that improve clinical outcomes.

For acute depression, the guideline recommends cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and behavioral activation as first-line treatments. Several interventions (see table, next page) were endorsed as second-line options. Long-term psychodynamic psychotherapy, acceptance and commitment therapy, videoconferenced psychotherapy, and motivational interviewing are reserved for third-line treatment. CBT and mindfulness-based cognitive therapy are recommended as first-line maintenance treatments, followed by IPT, behavioral activation, and cognitive-behavioral analysis system of psychotherapy (CBASP) as second-line choices. Evidence is insufficient to recommend most other psychological treatments as third-line options for maintenance.

When choosing an initial treatment, the availability of an evidence-based therapy should be a key consideration in patients who may be at risk from delaying treatment. For severe or

high-risk patients, it is imperative to start a treatment that is immediately available and to consider all options, including neurostimulation. For less severe and low-risk patients, the choice among psychological therapies and medication may be determined by the balance of patient preference and availability.

Recommendations for Acute and Maintenance Psychological Treatment for Depression		
Acute Treatments		
First-Line	Second-Line	
CBT IPT Behavioral Activation	CBASP Problem-solving therapy Short-term psychodynamic psychotherapy	Mindfulness-based cognitive therapy Telephone-delivered CBT and IPT Internet- and computer-assisted therapy
Maintenance Treatments		
First-Line	Second-Line	
CBT Mindfulness-based cognitive therapy	IPT Behavioral activation	CBASP

Research has shown that psychological therapies are equally effective in men and women, in patients of any age, ethnicity, and cultural and ethnic background, and in different subtypes of depression. As with medications, the magnitude of benefit increases with the severity of depression. A minimum dose of therapy has not been established, but many studies suggest psychological treatment can be effective with as few as 8 sessions. Group therapy is somewhat less effective than individual therapy but may be considered to extend the availability of treatment.

New to the guideline is a discussion of therapist factors associated with improved clinical outcomes. Those deemed "demonstrably effective" include empathy, a collaborative alliance based on agreement and an emotional bond, and monitoring treatment response with standardized scales. Other therapist factors deemed "probably effective" include a consensus on treatment goals, collaboration between therapist and patient, and positive regard (i.e., the patient's feeling that he or she is respected and appreciated).

Parikh S, Quilty L, Ravitz P, Rosenbluth M, et al: Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 2: psychological treatments. *Canadian Journal of Psychiatry* 2016; doi 10.1177.0706743716659418. From the University of Michigan, Ann Arbor; and other institutions. **Funded with internal CANMAT funds. Eight study authors disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

Reference Guide

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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.

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PSYCHIATRY ALERTS NOS

ACT for Anorexia Nervosa	57
Hypochondriasis-Related Disorders	58
Imaging Marker for Bipolar Disorder.....	59
Occupational Therapy for Schizophrenia	55
Open Dialogue Program for Psychosis	56
Reference Guide	60

Volume VIII / October 2016 / Number 10

www.alertpubs.com

New CME Activities Have Been Released . . . Have You Enrolled?

Occupational Goal Intervention in Resistant Schizophrenia

In a pilot study, the Occupational Goal Intervention (OGI) method, a rehabilitation program that targets executive function, improved social and functional performance in patients with treatment-resistant schizophrenia.

Background: OGI is an occupational therapy program that targets executive function using learning strategies to improve daily functioning. Originally designed to treat functional deficits associated with traumatic brain injury, it has been adapted for patients with schizophrenia. It has not previously been evaluated in treatment-resistant schizophrenia.

Methods: Study participants were adults who had persistent psychotic symptoms despite ≥ 2 adequate trials of different antipsychotics and current treatment with clozapine (*Clozaril*). Participants were randomly assigned to receive OGI or to participate in organized craft activities on a comparable schedule. OGI consisted of 90-minute sessions, twice per week, for 15 weeks. Sessions involved 4 or 5 patients and included homework assignments. The program covered such activities as personal hygiene; housework; money management; transportation; social activities; and leisure. Both OGI and control interventions were administered by occupational therapists. The primary outcome measure was the Behavioural Assessment of the Dysexecutive Syndrome (BADS), a measure of executive function.

Results: Of the 30 patients randomized, 25 completed the study. The majority were single, male, and unemployed or retired. High baseline scores on the Positive and Negative Syndrome Scale (PANSS) indicated severe schizophrenia symptoms.

After treatment, participants in OGI showed significant improvement in executive function, as indicated by the BADS total score ($p=0.035$; effect size [ES],* 0.87). They also demonstrated significant improvement on 3 of the 6 BADS subscales, indicating greater ability to develop a plan and solve a new problem, formulate a strategy and extract implicit information from a situation, and plan and carry out a sequential series of visits to sites and obey rules. OGI

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treatment was also associated with improvement on a measure of functional status, with greater skills in time orientation, communication, and grooming. Particularly striking were family member and caregiver ratings of the patients' autonomy and living skills, which showed significant improvement in areas such as self-nourishment (ES, 0.72); personal hygiene (ES, 1.27); household activities (ES, 1.27); food preparation/storage (ES, 1.76); health maintenance (ES, 0.93); money management (ES, 1.72); transportation (ES, 0.74); and leisure (ES, 1.07). OGI was not associated with improvement in PANSS symptoms or in subscales measuring positive or negative symptoms or general psychopathology.

Discussion: Executive functioning, which is severely compromised in schizophrenia and is considered the strongest predictor of functional impairment and diminished social and professional participation, is emerging as a major target of psychosocial treatment for schizophrenia. This is an ongoing study, and additional results will be reported with a larger sample and longer follow-up.

Vizzotto A, Celestino D, Buchain P, Oliveira A, et al: A pilot randomized controlled trial of the Occupational Goal Intervention method for the improvement of executive functioning in patients with treatment-resistant schizophrenia. *Psychiatry Research* 2016;245:148–156. From the University of Sao Paulo School of Medicine, Brazil. **Funded by FAPESP, the Sao Paulo Research Foundation. One study author disclosed financial relationships with commercial sources; the remaining 7 authors declared no competing interests.**

*See Reference Guide.

New Care Model for Early-Onset Psychosis

The Open Dialogue crisis intervention and care program, developed in Finland, was successfully implemented in a feasibility study in U.S. patients with first-episode psychosis. The program was viewed positively by staff, patients, and families and appeared to be safe and clinically effective. However, there were substantial costs traditionally not covered by insurance and a large training investment.

Open Dialogue is a clinical model developed for young people experiencing acute psychosis or another psychiatric crisis. Services are provided in "network meetings," attended by a multidisciplinary clinical team and involving the patient, family, and other support providers. When first contacted, the team responds rapidly, often meeting with the patient at home. The participants develop a shared understanding of the patient's experience and what care is needed. Antipsychotics may be delayed or used at low doses or for shorter periods than is typical in the U.S.

The clinical approach of Open Dialogue involves 12 key elements, and it is described as "dialogic practice." In general, meetings involve multiple clinicians, focus on the patient's own experience, include multiple perspectives, and normalize all communications, including expressions reflective of psychosis. Clinicians "reflect" among themselves about treatment planning, with opportunities for all network members to comment. Uncertainty is tolerated as understanding evolves and the group moves slowly to a diagnostic paradigm.

A 5-year uncontrolled follow-up study in 42 Finnish patients found that most had a high level of function and only a few were still taking antipsychotics. In the U.S. feasibility study, the program consisted of a mobile crisis unit, available around the clock, and outpatient services. Study participants were 16 individuals, aged 14–35 years, experiencing psychotic symptoms. Participants presented for emergency services voluntarily or involuntarily and were able to provide informed consent. Of those enrolled, 8 patients received treatment with antipsychotic medications at intake and 11 had prior psychiatric hospitalizations. The mean duration of illness was 41 weeks. The program was evaluated using structured questionnaires at enrollment and after 3, 6, and 12 months.

During the study year, Open Dialogue meetings were held a mean of 12.5 times per patient (range, 5–28). Ratings of client satisfaction and perceptions of shared decision making were high. Patients and their families appreciated the openness of decision making, felt cared for, and appreciated that treatment was not just medication focused. Staff satisfaction was also high. Clinical outcomes were generally positive, with improvement in psychiatric symptoms, function, and need for care. Of the 14 patients who completed the study, 9 were in school or working at 1 year; 4 patients had 6 hospitalizations (2 involuntarily).

Per-person cost ranged from about \$5000 to \$10,000. Third-party reimbursement covered <25% of the costs, likely because meetings involved multiple clinicians, off-hours sessions, and travel time. However, the higher early costs may be justified by improved outcomes that result in longer-term savings.

Gordon C, Gidugu V, Rogers E, DeRonck J, et al: Adapting Open Dialogue for early-onset psychosis into the U.S. health care environment: a feasibility study. *Psychiatric Services* 2016; doi 10.1176/appi.ps.201600271. From Advocates, Framingham MA; and other institutions. **Funded by the Foundation for Excellence in Mental Health Care; and the Cummings Foundation. The authors declared no competing interests.**

Acceptance and Commitment Therapy for Anorexia Nervosa

In a randomized trial, acceptance and commitment therapy (ACT) was not superior to treatment-as-usual in patients with a spectrum of anorexia nervosa diagnoses. However, the study was underpowered to detect an effect of ACT due to poor recruitment and high attrition, and secondary study outcomes indicate the treatment may have promise.

Methods: Study participants were adults who had completed a 9- to 12-week daycare refeeding program at a regional eating disorder clinic. At the end of daycare, they continued to meet DSM-IV criteria for full, sub-threshold, or partial anorexia nervosa, with ≥ 2 of the 4 DSM-IV criteria. (These patients would meet the more inclusive DSM-5 criteria for anorexia nervosa). After completing daycare, patients were randomly assigned to ACT or treatment-as-usual. The ACT protocol was modified from an ACT treatment of substance abuse and addressed the proposed common processes that establish and maintain psychopathology among a variety of disorders. ACT consisted of 19 hour-long sessions covering 8 core topics and additional optional material. The control group received treatment-as-usual, consisting of support and any other treatment they sought spontaneously. Follow-up evaluations were carried out immediately after treatment, at 6, 12, 18, and 24 months, and again after 5 years. The primary efficacy outcome measures were body mass index (BMI) and the Eating Disorder Examination Questionnaire (EDE-Q), a self-report instrument that measures patient concerns with restraint, eating, and weight.

Results: The study enrolled 43 participants (1 man), far short of the planned sample of 120 required to show a medium effect size. Of 24 patients in the ACT group, only 14 were considered completers, with ≥ 16 therapy sessions. Both groups showed significant improvement at the end of treatment and continued to improve across the follow-up intervals. There were no significant differences in the main outcome measures between groups at any point.

For the study, good outcome was defined as a BMI of ≥ 19 and a score of ≤ 2.83 on the EDE-Q. At the end of treatment, 4 of 16 ACT patients and 2 of 17 controls reached good outcome (25% vs. 12%; odds ratio,* 2.5). Throughout early follow-up, differences in the rate of good outcome generally favored ACT, but odds ratios were smaller (1.5–1.6 at 6–18 months). However, among patients available for follow-up at 5 years, good outcome was observed in 9 of 16 ACT patients and 5 of 14 controls (56% vs. 36%; odds ratio, 2.7).

Discussion: The study results tentatively favor ACT over treatment-as-usual, but it is possible that the ACT participants may have been a select group, since they had a higher rate of attrition

than the controls. There remains no well-supported treatment for anorexia nervosa; the majority of clinical trials have found that candidate treatments are not superior to no treatment. They suggest that the situation calls for a re-conceptualization of anorexia nervosa, perhaps emphasizing biological and genetic causes and with emaciation as the cause of psychopathology.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial; however, neither treatment nor assessment was blinded.

Parling T, Cernvall M, Ramklint M, Holmgren S, et al: A randomised trial of acceptance and commitment therapy for anorexia nervosa after daycare treatment, including five-year follow-up. *BMC Psychiatry* 2016; doi 10.1186/s12888-016-0975-6. From Uppsala University, Sweden; and other institutions. **Funded by the Swedish Research Council; and the Marta and Nicke Nasvell Foundation. The authors declared no competing interests.**

*See Reference Guide.

Treating Hypochondriasis-Related Disorders

Exposure-based cognitive behavioral therapy was effective in treating somatic symptom disorder (SSD) and illness anxiety disorder (IAD), the 2 DSM-5 diagnoses that have replaced DSM-IV hypochondriasis. The therapy was equally effective whether it was therapist-assisted via internet, delivered by internet without therapist input, or conducted as bibliotherapy.

Methods: Study participants were Swedish adults, recruited from medical settings or the general media, who completed an online application and then a 35- to 60-minute diagnostic interview. Participants were required to meet DSM-5 criteria for SSD or IAD, have no serious somatic disorder, and to not be receiving psychological treatment. Eligible subjects were randomly assigned to 1 of the 3 interventions or a wait-list control group. The 3 treatments were identical in content, consisting of 12 units with homework and emphasizing exposure to illness anxiety-related situations and response prevention. Therapist-assisted therapy consisted of frequent emails and messaging, with the patient answering specific theoretical questions, reporting on exercises, and receiving therapist feedback. Patients using the unassisted internet program had no therapist contact, but rather answered the questions online. The bibliotherapy group received a 154-page booklet with program content and exercises. The primary efficacy outcome was measured with the 64-item Health Anxiety Inventory.

Results: A total of 132 patients were enrolled, 127 were assessed post-treatment, and 89 completed follow-up at 6 months. (The control group was crossed over to active treatment after 12 weeks and did not participate in late follow-up.) The vast majority of patients (86%) met criteria for SSD, and the rest for IAD. Patients in the therapist-assisted and bibliotherapy groups completed an average of 8.6 and 8.3 of the 12 modules, respectively, while those in the internet-only group completed 6.6 units.

Participants in all 3 treatment groups experienced significant improvement, which persisted to the 6-month follow-up. Effects did not differ among the 3 active treatments, and all were superior to the control condition ($p < 0.001$ for the 3 treatment groups vs. control). Effect sizes* at 6 months, compared with baseline, were 2.23 for therapist-guided internet, 1.52 for unguided internet, and 1.61 for bibliotherapy. At 6-month follow-up, the proportions of patients in remission were 53%, 48%, and 44% for the 3 active treatments, respectively. The number needed to treat* per remission was about 2 for all active treatments.

Secondary outcome measures, including complementary measures of health anxiety and scales for general anxiety and depression, generally showed improvement with active

treatment. Patients reported high levels of satisfaction, which did not differ among treatments. The most commonly reported adverse effect of treatment was increased anxiety, affecting <20% of patients.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial. However, because of the nature of the interventions and the self-report format of the primary outcome measure, treatment and evaluation could not be provided in a blinded fashion.

Hedman E, Axelsson E, Andersson E, Lekander M, et al: Exposure-based cognitive-behavioural therapy via the internet and as bibliotherapy for somatic symptom disorder and illness anxiety disorder: randomised controlled trial. *British Journal of Psychiatry* 2016; doi 10.1192/bjp.bp.116.181396. From the Karolinska Institutet, Stockholm, Sweden. **Funded by the Karolinska Institutet; and the Stockholm County Council. The authors declared no conflicts of interest.**

*See Reference Guide.

Brain Imaging Marker for Bipolar Disorder

In a clinical sample of patients, diffusion tensor imaging, an MRI technique that examines the density of myelinated fibers in white matter tracts, identified a marker that distinguished non-manic patients with bipolar disorder from those with depression and healthy controls. The marker may be indicative of myelin damage of the corpus callosum, a mechanism that could underlie emotional dysregulation in bipolar disorder.

Methods: Study participants were 62 adults—16 with bipolar disorder, 23 with major depressive disorder, and 23 age- and gender-matched healthy controls. All patients were either euthymic or experiencing a depressive episode. All participants underwent standardized symptom and cognitive measures on the day of neuroimaging: the Young Mania Rating Scale, Montgomery-Asberg Depression Rating Scale (MADRS), and mini-mental state examination. Participants underwent diffusion-weighted MRIs, and the data were analyzed to show differences between patients with bipolar disorder and those with unipolar depression in fractional anisotropy (FA) in spherical regions of interest.

Results: The 2 patient groups did not differ significantly in age, gender, age at illness onset, or duration of illness. Patients with unipolar major depressive disorder had somewhat higher MADRS scores than patients with bipolar disorder. All patients with bipolar disorder were taking lithium or other mood stabilizers, as were 3 patients with major depression. Use of other psychotropic drugs, including antidepressants, did not differ between the 2 patient groups. Using a MADRS cutoff of 12 points to identify depression, 7 of the 16 patients with bipolar disorder and 17 of the 23 patients with unipolar depression were above the cutoff (44% vs. 74%); 9 and 6 patients, respectively, were euthymic.

Patients with bipolar disorder showed significantly lower FA values than those with unipolar depression ($p < 0.001$) and healthy controls ($p < 0.05$) in only 1 brain region, the anterior part of the corpus callosum. The difference between groups persisted after controlling the analysis for affective state (depressed vs. euthymic). FA values in unipolar depression patients did not differ from those in healthy volunteers. The investigators identified a cutoff FA value that correctly predicted 13 of 16 patients with bipolar disorder and 17 of the 23 patients with major depressive disorder, for a correct classification rate of 77%. The sensitivity* of the cutoff for bipolar disorder was 81%, and the specificity* was 74%.

Discussion: This is the first study to directly compare FA values between patients with unipolar major depression and those with bipolar disorder. The present observation, which requires replication in a larger sample, suggests patients with bipolar disorder may suffer a disruption of myelin in the corpus callosum, a white-matter structure that links the 2 brain

hemispheres. The disruption may signal a reduced number of oligodendrocytes linking left- and right-hemisphere prefrontal areas involved in emotional regulation.

Matsuoka K, Yasuno F, Kishimoto T, Yamamoto A, et al: Microstructural differences in the corpus callosum in patients with bipolar disorder and major depressive disorder. *Journal of Clinical Psychiatry* 2016; doi 10.4088/JCP.15m09851. From Nara Medical University, Japan; and other institutions. **Funded by the Japan Society for the Promotion of Science; and the Japan Ministry of Health, Labour, and Welfare. The authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

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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PSYCHIATRY ALERTS NOS

Curcumin for Depression	62
Dynamic Psychotherapy for Depression.....	65
Lipids in Schizophrenia	64
Psychosis Risk Calculator	63
Reference Guide	66
Saffron for Anxious Depression	61

Volume VIII / November 2016 / Number 11

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New CME Activities Have Been Released . . . Have You Enrolled?

Saffron Extract for Anxious Depression

In a 6-week randomized trial in patients with mild-to-moderate depression and anxious distress, saffron (*Crocus sativus* L.) was safe and had similar efficacy to citalopram (*Celexa*).

Methods: Study subjects (n=60; mean age, 36 years) met criteria for DSM-5 major depressive disorder with anxious distress. Patients' depression and anxiety were required to be of mild-to-moderate severity, with scores of <19 on the 17-item Hamilton Rating Scale for Depression (HAM-D) and <24 on the 14-item Hamilton Anxiety Rating Scale (HAM-A). Those with recent antidepressant use or ECT were excluded, as were those receiving regular aspirin, NSAIDs, or anticoagulants (because high-dose saffron is believed to induce bleeding). Patients were randomly assigned to receive either 40 mg/day citalopram or 30 mg/day saffron. The saffron capsules were commercially available standardized extracts of *Crocus sativa* stigma. Depression and anxiety were evaluated at study weeks 2, 4, and 6. The primary outcome was overall change from baseline in HAM-D and HAM-A scores. Secondary outcomes included rates of response ($\geq 50\%$ reduction in HAM-D score) and remission (HAM-D score ≤ 7).

Results: Patients in both groups had statistically significant decreases in HAM-D and HAM-A scores by week 6 ($p < 0.001$ for both endpoints in both groups). Changes from baseline were statistically significant beginning at week 2 for both outcomes and both treatments. Average HAM-D and HAM-A scores did not differ between the 2 groups at any time point. At 6 weeks, response criteria were met by 27 citalopram-treated patients and 22 saffron-treated patients (90% vs. 73%; $p = ns$). Remission occurred in 26 patients who received citalopram and in 19 who received saffron (87% vs. 63%; $p = ns$). Average times to response and remission in the entire study group were 5–6 weeks. Headache and nausea/vomiting, each affecting 2 patients, were the only adverse events observed with saffron.

Discussion: SSRIs are accepted as first-line treatment for depression with anxious distress. However, targeting multiple neuroendocrine systems may be a more effective approach. Saffron may act by inhibiting reuptake of serotonin, norepinephrine, and dopamine, as an

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NMDA receptor antagonist, and as a GABA- α agonist. Saffron also has cardioprotective effects, including improving lipid profiles, lowering blood pressure, and inhibiting atherosclerotic plaque formation. Despite limitations of the present study, including small sample size, fixed-dose design, and short duration of treatment, the results indicate saffron treatment may be a useful option for anxious depression.

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

Ghajar A, Neishabouri S, Velayati N, Jahangard L, et al: *Crocus sativus* L. versus citalopram in the treatment of major depressive disorder with anxious distress: a double-blind, controlled clinical trial. *Pharmacopsychiatry* 2016; doi 10.1055/s-0042-116159. From Tehran University of Medical Sciences, Iran. **Funded by Tehran University of Medical Sciences. The authors declared no competing interests. See related stories in *Psychiatry Alerts NOS* 2011;3 (May):28–29; and 2013;5 (December):67–68.**

*See Reference Guide.

Curcumin for Depression

In a placebo-controlled trial, curcumin, which is derived from the spice turmeric, had anti-depressant and anxiolytic effects in patients with major depressive disorder. The addition of saffron (*Crocus sativa* L.) did not enhance the effects of curcumin.

Methods: Study participants were adults, aged 18–65 years, with a DSM-IV diagnosis of major depressive disorder and an Inventory of Depressive Symptomatology, self-report (IDS-SR) score of ≥ 18 . Patients with atypical depression were not excluded, but comorbid bipolar disorder, psychosis, OCD, and PTSD were exclusion criteria. Following a 1-week placebo lead-in, patients were randomly assigned to 1 of 4 double-blind treatments: placebo, low-dose curcumin (250 mg b.i.d.), high-dose curcumin (500 mg b.i.d.), or low-dose curcumin plus 15 mg saffron b.i.d. All active agents were provided as capsules containing standardized extracts. Treatment was continued for 12 weeks; concomitant treatment with stable antidepressant medication was permitted. The primary outcome measure was change from baseline on the IDS-SR. Anxiety, a secondary outcome, was measured with the Spielberger State-Trait Anxiety Inventory (STAI).

Results: Of 123 patients who completed the placebo run-in and were randomly assigned to a treatment, 111 completed all study requirements. The largest number of dropouts, 5 patients, was in the placebo group. About half of all study patients took antidepressants at baseline and during the trial.

IDS-SR scores improved significantly over time in all 4 treatment groups ($p < 0.001$ for all treatments at 12 weeks vs. baseline). Improvement was limited to the first 4 weeks in the placebo group but continued throughout treatment in the other groups. Results in the combined active treatment groups were superior to placebo ($p = 0.031$). There were no differences in the mean change in the IDS-SR among patients who received low-dose curcumin, high-dose curcumin, or curcumin with saffron. The rates of response ($> 50\%$ reduction in the IDS-SR score) were greater in the active treatment groups combined than in the placebo group (28% vs. 13%), but the difference failed to reach statistical significance. Scores on the STAI subscales measuring state and trait anxiety were also reduced to a greater degree in the combined active treatments group, compared with placebo.

A separate analysis was carried out comparing 34 patients with atypical depression and 46 with other depression. In this comparison, the combined active treatments were significantly superior to placebo with regard to the IDS-SR ($p = 0.007$), state anxiety ($p < 0.001$), and trait anxiety ($p = 0.009$). Response occurred in 65% of patients with atypical depression and in 35% of those with other types ($p = 0.012$). Only minor adverse events were reported.

Discussion: Previous studies of curcumin have shown an antidepressant effect with a 500-mg b.i.d. dose. This study suggests a lower dose may be equally effective. Anti-anxiety effects are also a new finding. The efficacy in atypical depression may be attributable to the presence of elevated inflammatory markers in this subtype, as curcumin has potent anti-inflammatory effects.

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

Lopresti A, Drummond P: Efficacy of curcumin, and a saffron/curcumin combination for the treatment of major depression: a randomised, double-blind, placebo-controlled study. *Journal of Affective Disorders* 2017;207 (January):188–196. From Murdoch University, Perth, Australia. Funded by Arjuna Natural Extracts Ltd.; and other sources. The authors declared no competing interests.

*See Reference Guide.

Risk Calculator for Psychosis

A research group on prodromal psychosis has developed an individualized risk calculator to improve the prediction of conversion of high-risk individuals to psychosis within 2 years.¹ The risk calculator is comparable in accuracy to those available for some medical illnesses.

Methods: The second phase of the North American Prodrome Longitudinal Study (NAPLS-2) follows a cohort of adults identified as at risk for psychosis based on the presence of ≥1 clinical high-risk syndromes identified using the Structured Interview for Prodromal Syndromes (SIPS): attenuated psychotic symptoms syndrome, brief intermittent psychotic symptom syndrome, and familial risk and deterioration syndrome. The investigators identified 8 predictor variables for conversion, based on the published literature and on the ability to easily ascertain the factors in clinical practice. (See table.) They then developed a model using the 8 factors to predict risk of conversion in 596 participants in the NAPLS-2 cohort who had ≥1 follow-up evaluation within 2 years of qualifying.

Results: The 596 study participants had a mean age of 18.5 years at baseline. A total of 84 converted to psychosis within 2 years, another 280 were followed for 2 years without converting, and the rest were lost to follow-up at various points between 6 and 24 months.

The overall 2-year probability of converting to psychosis was 16%. Of the 8 individual factors, prodromal symptom severity, decline in social functioning, and verbal learning and memory scores were statistically significant predictors in multivariate models, while age at baseline and

processing speed were significant only in univariate models. The remaining factors—stressful life events, traumas, and family history—were not significant predictors of transition to psychosis. However, these

Characteristics incorporated in the NAPLS-2 risk calculator in prodromal psychosis	
Characteristic	Measurement
Age at ascertainment	Self report
Unusual thought content/suspiciousness	SIPS items P1 and P2
Slower processing speed	Brief Assessment of Cognition in Schizophrenia
Lower verbal learning/memory function	Hopkins Verbal Learning Test–Revised
Decline in social functioning	Global Functioning: Social Scale
Stressful life events	Research Interview Life Events Scale
Childhood trauma	Childhood Trauma and Abuse Scale
Family history of psychosis	Presence in first-degree relative

factors are present more frequently in high-risk individuals, possibly suggesting they are better markers for the presence of high risk and less sensitive as a marker for transition in an already identified high-risk group.

Discussion: An online version of the calculator is available at <http://riskcalc.org:3838/napls/>. The calculator has a C-index (ability to discriminate accurately) of 0.71. For comparison, the probability of correctly identifying converters by chance is 0.5, and online calculators for cardiovascular or cancer risk have C-indexes in the range of 0.6 to 0.8. The authors and an accompanying editorial² recommend use of the calculator to identify subjects for clinical trials of preventive measures, which would increase the studies' efficiency and spare individuals who are unlikely to benefit from these interventions. Clinical use is best limited to clinicians with expertise in using SIPS and the other structured questionnaires who can provide treatment recommendations. The calculator is not yet recommended for general clinical use and includes safeguards to limit access by untrained users.

¹Cannon T, Yu C, Addington J, Bearden C, et al: An individualized risk calculator for research in prodromal psychosis. *American Journal of Psychiatry* 2016;173 (October):980–988. From Yale University, New Haven, CT; and other institutions. **Funded by the NIH. Four study authors declared financial relationships with commercial sources; the remaining 12 authors declared no competing interests.**

²Carpenter W: Early detection of psychosis vulnerability: progress, opportunity, and caution [editorial]. *American Journal of Psychiatry* 2016;173 (October):949–950. From the University of Maryland, Baltimore. **The author disclosed financial relationships with commercial sources.**

Lipid Profiles and Clinical Traits in Schizophrenia

In a longitudinal study of patients with schizophrenia, membrane lipid levels fluctuated with disease course, while serum lipid elevation appeared to be a stable disease trait. These findings suggest abnormal lipid metabolism may be involved in the pathophysiology of schizophrenia and may be a useful biomarker.

Methods: Study participants were 55 patients with schizophrenia or schizoaffective disorder, recruited as part of a larger study of nutritional supplements in the disorders. At enrollment, patients had been admitted to an emergency psychiatric ward and were considered acutely ill. Patients were evaluated again 5 years later during treatment for chronic disease at outpatient clinics or in long-term care facilities. They were assessed clinically at both times using the Positive and Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF), and lipids were measured at both visits. Serum and membrane lipids were also measured in a control group of individuals with no personal or family history of a severe psychiatric illness. Membrane lipids were measured in 20 controls at baseline and a partially overlapping group of 51 controls 5 years later. Serum lipids were only measured in controls at the second time point.

Results: At enrollment, patients had a mean age of 27 years. No patient or control used medication for dyslipidemia. About half of patients used antipsychotic medication before emergency admission, all 55 used antipsychotics when admitted, and 80% were using these medications 5 years later. Average GAF scores showed significant improvement between the first and second evaluation, but mean PANSS scores did not change over time.

Both at baseline and after 5 years, serum triglyceride levels were significantly higher in patients than in controls ($p < 0.001$ for both). Serum cholesterol was similar in patients and controls. The patients' mean serum lipid levels did not change over the 5 years.

At the first evaluation, average membrane lipids were significantly lower in patients than controls, both for polyunsaturated fatty acids (PUFA) and long-chain PUFA ($p < 0.001$ for both). Five years later, levels of both membrane lipids did not differ between patients and

controls. PUFA levels showed a bimodal distribution (defining a high and low PUFA group) in patients at baseline and a normal distribution at the second time point. A significant increase in PUFA levels at 5 years was driven by an increase in patients who initially had low membrane PUFA levels.

There was no significant association between patients' lipid levels and symptoms at the acute stage. However, in the chronic stage, both serum and membrane lipid levels were associated with PANSS and GAF scores, with higher levels associated with more severe symptoms. High serum lipids at baseline were also associated with more severe symptoms in the chronic stage.

Discussion: Dyslipidemia, long regarded as a result of behavior and/or antipsychotic medication, is increasingly being recognized as a disease trait and possibly an underlying mechanism of schizophrenia. The present observations, which include the frequent lack of antipsychotic treatment at baseline, suggest serum triglyceride elevation may be a core mechanism of schizophrenia. Membrane lipids appear to fluctuate in different disease states and may be a marker for inflammatory processes.

Solberg D, Bentsen H, Refsum H, Andreassen O: Lipid profiles in schizophrenia associated with clinical traits: a five year follow-up study. *BMC Psychiatry* 2016; doi 10.1186/s12888-016-1006-3. From the Norwegian Defense Medical Services, Oslo; and other institutions. **Funded by the Eastern Norway Regional Health Authority; and other sources. The authors declared no competing interests.**

Dynamic Psychotherapy for Depression

According to results of a randomized noninferiority trial, efficacy of short-term dynamic psychotherapy, a technique that targets the individual's impairing relationship conflicts, is similar to that of cognitive therapy (CT) in patients with unipolar major depressive disorder.¹ This trial addresses the substantial debate that surrounds the efficacy of short-term dynamic psychotherapy.

Methods: Dynamic psychotherapy and CT were compared in a randomized trial conducted in an outpatient community mental healthcare center. Participants were adults who met DSM-IV criteria for major depressive disorder (including those with substance use problems but not those requiring urgent treatment) who sought services at the center. Dynamic psychotherapy consisted of expressive techniques to help patients understand their repetitive maladaptive relationship patterns. CT focused on behavioral activation and exploration of depressogenic beliefs. Both treatments were delivered in 16 sessions over 5 months. The primary outcome was change from baseline in Hamilton Rating Scale for Depression (HAM-D) score.

Results: A total of 237 study subjects (mean age, 36 years; 75% women) were randomized to treatment. Nearly 90% of participants had a concurrent Axis-I diagnosis, 70% had concurrent anxiety, and 56% had an alcohol or substance use disorder. One-fourth of enrolled participants attended only 1 session of therapy, and half attended ≤ 5 sessions.

Average HAM-D scores decreased from about 21 at baseline to 16 at study end in the 2 treatment groups, with no significant difference between them (effect size,* 0.11). The use of psychotropic medication did not affect the comparison of treatments. Secondary outcomes, including function, quality of life, and self-rated depression, did not differ between the 2 groups, although the study lacked sufficient statistical power to compare these outcomes. Response, defined as a $\geq 50\%$ reduction in HAM-D score, occurred in 19 patients (16%) with dynamic therapy and in 26 (22%) with CT.

Editorial.² Although these results suggest that dynamic psychotherapy is as effective as cognitive therapy in the treatment of depression, response rates with both therapies were

low. Adherence to treatment and therapist competence were high in this study, and non-response may be partly explained by inadequate treatment dose, or unmeasured clinical sample characteristics, biomedical factors, and/or sociofamilial factors.

¹Gibbons M, Gallop R, Thompson D, Luther D, et al: Comparative effectiveness of cognitive therapy and dynamic psychotherapy for major depressive disorder in a community mental health setting: a randomized clinical noninferiority trial. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.1720. From the University of Pennsylvania, Philadelphia; and NHS Human Services, Erdenheim, PA. **Funded by the Agency for Healthcare Research and Quality. The authors declared no competing interests.**

²Abbass A, Town J: Bona fide psychotherapy models are equally effective for major depressive disorder: future research directions [editorial]. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.1916. From Dalhousie University, Canada; and other institutions. **The authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

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PSYCHIATRY ALERTS NOS

CBT for Resistant Anxiety	70
OCD: Patient Treatment Preferences	69
Reference Guide	72
Suicide After Hospital Discharge	68
Taurine in Psychosis.....	71
Virtual Hope Box.....	67

Volume VIII / December 2016 / Number 12

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New CME Activities Coming Soon . . . Have You Enrolled?

Smartphone App for Emotional Regulation

In a randomized trial, U.S. service veterans with suicidal ideation who used a Virtual Hope Box (VHB) smartphone app were better able to cope with negative emotions.

Background: Clinicians often use a physical "hope box" to help patients cope with distress or suicidal ideation. The VHB is an electronic adaptation that uses smartphone technology to create a virtual container of items that remind the person of positive life experiences, people who care, coping or distracting resources, or reasons for living. An important rationale for development of the VHB was to extend the use of an already established, effective intervention. The app is available as a free download for both Android and iPhones.

Methods: Study participants were U.S. military veterans in active mental-health treatment and expressing suicidal ideation currently or in the past 3 months. They were randomly assigned to receive either the VHB, added to treatment as usual, or enhanced treatment as usual with the addition of printed information about coping with suicidal thoughts and other prevention resources. Patients who received the VHB met with a clinician for instruction in using the app and individual tailoring of its content. Those in the control group also received personal guidance from a clinician. The primary outcomes, measured at 3, 6, and 12 weeks, included 2 subscales from the Coping Self-Efficacy Scale (CSE) indicating the ability to stop unpleasant emotions and thoughts and to enlist support from friends and family. Suicidal ideation was measured with a brief version of the Beck Scale for Suicide Ideation. Scores on the Brief Reasons for Living Inventory (BRFL) were an additional primary outcome.

Results: The 118 study participants were in their late 40s on average; about one-third were women; about 80% were currently or recently taking antidepressants; and three-fourths had a service-related disability.

All outcomes improved over the 12 study weeks in both treatment groups. Patients who used the VHB had significantly greater improvement than the control group in the "stop unpleasant

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emotions and thoughts" subscale of the CSE, which was statistically significant at weeks 3 and 12. Scores on the "enlist support from friends and family" subscale did not differ between the groups. Suicidal ideation scores decreased substantially with no difference between the groups. Small and similar improvements were seen in both groups on the BRFL measure.

Participants who used the VHB reported that the intervention was helpful and that they intended to use it again or recommend it. The most frequent reasons for using it were for distress (69%), to deal with overwhelming emotions (57%), when they felt like hurting themselves (31%), and for relaxation, distraction, or inspiration (51%). Clinicians said that they appreciated the VHB as an additional therapeutic tool allowing patients to practice their coping skills.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial; however, the nature of the treatment and the use of primarily self-report efficacy measures precluded blinding.

Bush N, Smolenski D, Denneson L, Williams H, et al: A Virtual Hope Box: randomized controlled trial of a smartphone app for emotional regulation and coping with distress. *Psychiatric Services* 2016; doi 10.1176/appi.ps.201600283. From the U.S. Department of Defense, Joint Base Lewis-McChord, Tacoma, WA; and other institutions. **Funded by the Military Suicide Research Consortium. The authors declared no competing interests.**

*See Reference Guide.

Disorder-Specific Risks of Post-Discharge Suicide

A large cohort study, undertaken to identify disorder-specific risks and other factors that may help predict which inpatients are at risk for suicide after discharge, found that short-term risk of suicide was highest in patients with a primary diagnosis of depression, followed closely by those with bipolar disorder.¹

Methods: The study cohort consisted of nearly 2 million adults, aged 18–64 years, covered by Medicaid between 2001 and 2007 and discharged after being psychiatrically hospitalized for ≤30 days. To investigate the role of preadmission psychiatric care, cohort members were required to have been eligible for Medicaid services during the 6 months before admission. A comparison group consisted of a 10% random sample of Medicaid enrollees with acute hospitalizations for non-psychiatric diagnoses. The outcome of interest was suicide within 90 days after discharge. Suicide rates were compared among patients discharged with a psychiatric diagnosis, those discharged with other diagnoses, and the general U.S. population, matched for age, gender, race/ethnicity, and region.

Results: The cohort consisted of >770,000 patients discharged with a mental-illness diagnosis and >1 million in the comparison group. Short-term suicide rates were elevated in patients discharged with a mental-health diagnosis (rate, 178 per 100,000 person-years), with an approximately 13- to 15-fold increase compared with the non-psychiatric Medicaid cohort and the general U.S. population. Among patients discharged with a mental-health diagnosis, suicide rates were highest in those with depression (235 per 100,000 person-years; hazard ratio,* 13) or bipolar disorder (216 per 100,000 person-years; hazard ratio, 11.1), followed by schizophrenia (168 per 100,000 person-years; hazard ratio, 8.9), and lowest in those with a substance use disorder (117 per 100,000 person-years; hazard ratio, 6.6). Suicide rates were nearly twice as high in men as in women and higher in young adults (aged 18–34 years) than other age groups. Risk was also elevated in patients who lacked a history of outpatient health care in the 6 months before admission (adjusted hazard ratio, 1.7).

Discussion: Other research has shown that an absence of treatment before psychiatric hospitalization is strongly associated with treatment disengagement after hospital discharge, probably increasing the short-term risk of suicide. An absence of prior care should alert inpatient psychiatrists to the need to coordinate patients' follow-up care.

Editorial.² Suicide risk assessments are controversial in nature and have low predictive value. Development of semi-structured checklist-style instruments that could provide guidance in interviewing patients at the time of discharge would be useful in suicide prevention. In addition, outpatient referrals should be before discharge and treatment should be started early, so that patients will be familiar with their new providers before discharge. The particularly pronounced increase in suicide in the week after discharge indicates a need to ensure continuity by making the first follow-up appointment while the patient is still hospitalized.

¹Olfson M, Wall M, Wang S, Crystal S, et al: Short-term suicide risk after psychiatric hospital discharge. *JAMA Psychiatry* 2016;73 (November):1119–1126. From Columbia University, New York, NY; and other institutions. **Funded by the Agency for Healthcare Research and Quality; and New York State Psychiatric Institute. The authors declared no competing interests.**

²Nordentoft M, Erlangsen A, Madsen T: Postdischarge suicides: nightmare and disgrace [editorial]. *JAMA Psychiatry* 2016;73 (November):1113–1114. From the Mental Health Centre Copenhagen, Denmark; and other institutions. **The authors declared no competing interests.**

*See Reference Guide.

Patient Preference for OCD Treatment

According to results of an analysis of an online survey, patient preference of treatment for obsessive-compulsive disorder is influenced by individual characteristics such as age, gender, income, insurance, and treatment experience.¹ Overall, respondents showed a modest preference for exposure and response prevention (EX/RP) over medication as first-line therapy.

Methods: Adults seeking information on the website of a university-based OCD clinic were invited to complete a 30-minute survey on preferences for treatment. The survey included the Obsessive-Compulsive Inventory–Revised (OCI-R), an 18-item self-report questionnaire; information was also obtained about demographic factors, treatment history, preferences among existing evidence-based treatments, and acceptability of several novel treatments. All treatment options were accompanied by a description (vetted by an expert in that treatment) of what the treatment entailed, typical duration, efficacy, and possible side effects. Participants who reported residual symptoms when taking an SRI were also asked about their preference for augmentation treatment. At the end of the survey, participants were provided an open-ended opportunity to discuss their opinions.

Results: A total of 304 surveys were completed. Of the 216 respondents who self-reported OCD symptoms, 71% reported clinically significant symptoms on the OCI-R and 85% reported that they had received a diagnosis of OCD from a medical professional. The mean score on the OCI-R indicated severe OCD symptoms. The mean respondent age was 34 years, 73% were women, 75% had private insurance, and 13% were uninsured.

In the survey, SRIs and EX/RP were offered as choices for first-line treatment; 55% of patients preferred EX/RP, and 45% preferred SRIs, a statistically nonsignificant difference. Preference for SRIs was associated with current use of the drugs and a positive experience with treatment overall. In a forced choice between EX/RP and antipsychotics for second-line treatment, 68% of patients with residual symptoms chose EX/RP. Patients who preferred second-line EX/RP were younger on average and more likely to be women.

A latent class analysis* identified 2 distinct classes of patient. One class, consisting of about 55% of participants, was more likely to have higher income, private insurance, and a diagnosis of OCD and to be currently receiving treatment for OCD. This class of patients had a higher likelihood to prefer SRI therapy. Among novel treatments, acceptance and commitment therapy received the highest acceptability rating (73%), followed by Kundalini yoga

(58%). The other options, in descending order of acceptability, were glutamate modulating medications, transcranial magnetic stimulation, gamma knife surgery, and deep brain stimulation. In the open-ended part of the survey, participants most frequently expressed a desire for educating the public about OCD and increasing access to treatment.

Discussion: The finding that adults with OCD prefer EX/RP over medication as a first-line treatment is consistent with previous research in a smaller sample of patients.² However, nationwide treatment utilization data indicate that patients with OCD more commonly receive treatment with medications than with psychotherapy. Efforts to increase access to psychotherapy including EX/RP are needed.

¹Patel S, Galfavy H, Kimeldorf M, Dixon L, et al: Patient preferences and acceptability of evidence-based and novel treatments for obsessive-compulsive disorder. *Psychiatric Services* 2016; doi 10.1176/appi.ps.201600092. From Columbia University, New York, NY, and other institutions. **Funded by the NIMH and the New York State Office of Mental Hygiene. One author disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

²Patel S, Simpson H: Patient preferences for obsessive-compulsive disorder treatment. *Journal of Clinical Psychiatry* 2010; 71:1434–1439. See *Psychiatry Alerts* NOS 2010;2 (November):67–68.

*See Reference Guide.

Adjunctive CBT for Resistant Anxiety

Cognitive behavioral therapy improved rates of response and remission in patients whose anxiety symptoms had not responded to pharmacotherapy, according to a secondary analysis of data from a clinical trial.¹

Background: The primary aim of the trial was to test the efficacy of the Coordinated Anxiety and Learning Management (CALM) CBT intervention. The computer-assisted CALM intervention, designed to approximate anxiety treatment in clinical practice, consists of individualized CBT that can be adapted to any of the 4 most common anxiety disorders in primary care: generalized anxiety disorder, PTSD, panic disorder, and social anxiety disorder. According to a previous report of the main trial results,² CALM was more effective than usual care in relieving anxiety symptoms.

Methods: The present analysis was limited to CALM trial participants who were classified as medication resistant on the basis of their medication history before entering the trial. Medication resistance was defined as current use of appropriate medications (which were specific for each disorder) at adequate doses for ≥ 2 months. Of 227 patients with drug-resistant anxiety disorders, 117 were randomized to the CALM intervention and 110 to the usual-care control condition. Patients assigned to the CALM group were offered the choice of CALM, medication management, or both, and all but 10 patients chose to receive the CALM intervention. Based on results of the larger study, high-dose CALM-CBT was defined as ≥ 6 sessions. Usual care consisted of primary care, which could include medication management and referral for CBT or other forms of therapy. The primary efficacy outcomes were response, defined as a $\geq 50\%$ reduction in scores on the 12 anxiety and somatic symptom items on the Brief Symptom Inventory (BSI-12); and remission, defined as a BSI-12 total score < 6 or average scores in the none or mild range for all items.

Results: At 18 months follow-up, rates of response and remission were higher with CALM-CBT than usual care at most time points. (See table.) Within the CALM-CBT group, 38 of 56 initial (6-month) responders retained their response at 1 year and 10 additional patients achieved response. An additional 4 patients achieved response by 18 months. Of 54 CALM-CBT patients who had not achieved remission at 6 months, 11 achieved remission by 12 months and an additional 3 by 18 months. Three-fourths of patients received a minimum of 6 CALM-CBT sessions. When the analysis was limited to these patients, early rates of

response and remission were higher than in those who received fewer sessions, but 18-month results did not differ. The combination of medication with CALM-CBT did not offer any additional advantage over CALM-CBT alone.

Outcomes of CALM-CBT versus usual care in patients with anxiety disorders				
	CALM-CBT	Usual Care	Odds Ratio*	Significance
Response				
6 Months	58%	29%	3.78	p<0.001
12 Months	55%	33%	2.49	p=0.003
18 Months	58%	49%	1.55	p=NS
Remission				
6 Months	44%	22%	3.18	p<0.001
12 Months	47%	26%	2.55	p=0.004
18 months	46%	27%	2.44	p=0.006

¹Campbell-Sills L, Roy-Byrne P, Craske M, Bystritsky A, et al: Improving outcomes for patients with medication-resistant anxiety: effects of collaborative care with cognitive behavioral therapy. *Depression and Anxiety* 2016; doi: 10.1002/da.22574. From University of California San Diego, La Jolla; and other institutions. **Funded by the NIMH. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

²Roy-Byrne, P, et al: Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. *JAMA* 2010;303 (May 19):1921–1928. See *Psychiatry Alerts NOS* 2010; 2 (May):29–30.

*See Reference Guide.

Adjunctive Taurine in Psychosis

In a randomized trial, adjunctive taurine improved symptoms of psychosis in patients experiencing their first episode. However, cognitive performance was not improved.

Methods: Study participants were adults, aged 18–25 years, recruited from a center that specializes in treating first-episode psychosis. Patients with a diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, mood disorder with psychotic features, or psychosis NOS were all included provided they had received ≥ 3 months of treatment before study entry. Participants (n=86) were randomly assigned to receive adjunctive double-blind treatment with 4 g/day taurine or placebo for 12 weeks. All patients received standard clinical care, which included outpatient case management, family work, and group programs. The study had 2 primary efficacy outcomes: psychosis, measured with the Brief Psychiatric Rating Scale (BPRS), and cognition, measured using the MATRICS Consensus Cognitive Battery. The latter instrument consists of 10 tasks that measure 7 domains of cognition: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition.

Results: Participants had been receiving treatment for 9–10 months on average before randomization, and about two-thirds were receiving an antipsychotic medication at baseline. A total of 26% from the taurine group and 15% from the placebo group did not complete the 12-week assessment.

Change from baseline in the BPRS total score was significantly larger in the group receiving taurine than the placebo group (p=0.004, effect size,* 0.67). Taurine was also associated with greater improvement in the BPRS psychotic subscale, which encompasses the symptoms of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization

($p=0.026$; effect size, 0.49). Changes in score on the Calgary Depression Scale for Schizophrenia, Brief Psychiatric Rating Scale, and Global Assessment of Functioning also showed significant improvement with taurine relative to placebo, although the effect sizes were smaller (about 0.45). The treatment groups did not differ in changes from baseline in negative symptoms or cognition. Taurine had similar tolerability to placebo.

Discussion: Taurine is an amino acid that has an inhibitory neuromodulating effect in the CNS, via multiple mechanisms. Preliminary studies suggested it might improve both psychotic symptoms and schizophrenia-related cognitive deficits. In first-episode patients, taurine might be best used as a secondary add-on to antipsychotic medication, but further study is needed.

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

O'Donnell C, Allott K, Murphy B, Yuen H, et al: Adjunctive taurine in first-episode psychosis: a phase 2, double-blind, randomized, placebo-controlled study. *Journal of Clinical Psychiatry* 2016; doi 10.4088/jcp.15m10185. From Donegal Mental Health Service, Letterkenny, Ireland; and other institutions. **Funded by the Stanley Medical Research Institute. The authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

Latent Class Analysis: A statistical method used to find subtypes of related cases (latent classes) from multivariate categorical data. It can be used to find distinct diagnostic categories given presence/absence of several symptoms, types of attitude structures from survey responses, or subpopulations based on answers to test items.

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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Psychiatry Alerts NOS 2016 INDEX

A

acceptance and commitment therapy, 53, 57, 69
ADHD, 40
adherence therapy, 14
aggression, 22
alcohol addiction, 46
Alzheimer's disease, 13
anemia, 2
anorexia nervosa, 57
anxiety, 7, 9, 11, 35
anxiety, resistant, 70
aripiprazole, 16

B

behavioral activation therapy, 37, 53
benzoic acid, 26
bibliotherapy, 58
binge eating disorder, 49
biomarkers, 26, 32, 64
bipolar disorder, 20, 37, 45, 59
blue light, 45
brain imaging, 32, 59
bright light therapy, 17

C

chlorpromazine, 16
clozapine, 16
cognitive behavioral therapy, 10, 11, 17, 23, 25, 30, 53, 70
cognitive behavioral therapy, internet, 52
cognitive processing therapy, 34
cognitive therapy, 65
complement component 4 (C4) genes, 13
complicated grief treatment (CGT), 47
concussion, 19
Coordinated Anxiety and Learning Management CBT, 70
creatinine, 26
curcumin, 62

D

deep brain stimulation, 46, 70
depression, 3, 9, 10, 11, 13, 21, 23, 26, 29, 30, 31, 32, 38, 43,
51, 53, 59, 61, 62, 65
depression, anxious, 61, 62
depression, bipolar, 37
depression, caregiver, 25
depression, late-life, 27
depression, resistant, 7
dialogical exposure therapy, 4
diffusion tensor imaging, 59
domestic abuse, 28
dopamine, 26
dynamic psychotherapy, 65

E

ECT, 27
ECT, ultrabrief pulse, 51
escitalopram, 33
ethanolamine, 26
excoriation disorder, 20
exposure and response prevention, 4, 69
exposure-based cognitive behavioral therapy, 58
eye movement desensitization reprocessing, 34

F

folinic acid, 43
fumaric acid, 26

G

gamma knife surgery, 70
gamma-aminobutyric acid, 26
gamma-tocopherol, 26
generalized anxiety disorder, 39
genetics, 13
geriatric depression, 7
gestalt-based treatment, 4
glutamate, 50
gratitude writing, 41

H

haloperidol, 16
hoarding disorder, 23
homoserine, 26
human leukocyte antigen genes, 13
hydroxylamine, 26
hypochondriasis, 58

I

illness anxiety disorder, 58
iloperidone, 16
intermittent explosive disorder, 22
interpersonal therapy, 53
isoleucine, 26

L

lanosterol, 26
lavender oil, 9
lipid metabolism, 64

M

malic acid, 26
malonic acid, 26
mania, 45
masculine norms, 8
MDMA, 35

memory impairment, 23
methylfolate, 43
mindfulness-based cognitive therapy, 38, 53
motivational interviewing, 11, 14, 53

N

N-acetylcysteine, 20
negative symptoms, 27, 35
neurochemical markers, 13
nicotine replacement therapy, 5
nonsuicidal self-injury, 8
nutraceuticals, 43

O

obsessive-compulsive disorder, 3, 4, 35, 69
Occupational Goal Intervention, 55
octanoic acid, 26
olanzapine, 16
omega-3 fatty acids, 43
Open Dialogue crisis intervention and care program, 56

P

peripheral blood mononuclear cells, 26
postpartum psychosis, 20
prodromal psychosis, 63
prolonged exposure/imaginal exposure, 34
Psilocybin, 35
psychedelic drugs, 35
psychodynamic psychotherapy, 53
psychosis, 44, 56, 63, 71
PTSD, 15, 28, 33, 35, 44

Q

quetiapine, 16

R

relapse prevention, 38
relaxin receptors, 13
repetitive transcranial magnetic stimulation, 5, 29, 39
ribulose 5-phosphate, 26
risperidone, 16

S

saffron, 61
SAMe, 43

schizophrenia, 13, 14, 16, 27, 35, 50, 64
schizophrenia, treatment-resistant, 55
seasonal affective disorder, 17
second-generation antidepressants, 30
Self-evaluation of Negative Symptoms, 36
sertraline, 33
silexan, 9
smoking cessation, 5
social anxiety disorder, 52
social rhythm therapy, 15
somatic symptom disorder, 58
sorbitol, 26
SRIs, 69
Stress inoculation training, 34
substance-use disorders, 35
suicidal ideation, 67
suicide, 19, 44
suicide prevention, 1, 68

T

taurine, 71
Toxoplasma gondii infection, 22
transcranial direct current stimulation, 16, 27, 49
transcranial magnetic stimulation, 70
transcutaneous auricular vagus nerve stimulation, 21
trauma-focused psychotherapies, 33
traumatic brain injury, 11
treatment guidelines, 30, 53
trigeminal nerve stimulation, 7

V

valine, 26
venlafaxine, 33
videoconferenced psychotherapy, 53
Virtual Hope Box, 67
vitamin D, 43

W

whole-body hyperthermia, 31

Y

yoga, 69