

PSYCHIATRY ALERTS NOS 2018 VOLUME 10

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.

January 2018

Alpha-Lipoic Acid in Schizophrenia, 3
CBD in Schizophrenia, 2
ECT for Dementia-Related Agitation, 5
Internet-Based CBT for Bulimia, 3
Urine Screening Recommendations, 1
Web-Based Treatment for Depression, 4

February 2018

Adaptive DBS for Tourette's, 8
Botulinum Toxin for Depression, 11
EMDR for Substance Use Disorder, 10
E-Prescribing and Medication Errors, 10
Social Recovery Therapy for Psychosis,
7 tDCS for Bipolar Depression, 9

March 2018

Behavioral Avoidance in OCD, 16
Brain Stimulation for Substance Use Disorders, 13
Computer-Assisted CBT for Depression, 15
Inflammatory Marker and ECT Response, 17
Virtual Reality Treatment for Paranoia, 15
VNS: Long-Term Effects on Depression, 14

April 2018

Aggression and Creatine Kinase Levels, 22
Bipolar Conversion Predictors, 19
CET plus tDCS for Resistant Depression, 23
Depression Relapse and Brain Morphology,
21 Mental Health Apps: Evaluation, 20
Schizophrenia: Gene Mapping, 23

May 2018

DBS for Depression, 26
Depression, Anxiety, and Thyroid Disease, 29
ECT and Dementia Risk, 27
Preventive Cognitive Therapy in Depression, 28
rTMS for Suicidal Ideation, 25

June 2018

Circadian Activity and Mood, 35
Ketamine Anesthesia for ECT, 31
mHealth for Serious Mental Illness, 33
Nightmare Disorder Treatments, 34
TMS plus Behavioral Activation Therapy, 32

July 2018

Cognitive/Exposure Therapy for Hoarding, 40
Mantram Repetition for PTSD, 38
Mitochondrial Agents for Bipolar Disorder, 40
PRIME App for Schizophrenia, 37
Psychoeducation in Bipolar Disorder, 39
rTMS for Anxiety/Insomnia, 41

August 2018

Binge Eating Disorder Treatments, 47
Image-Focused Therapy in Bipolar Disorder, 44
Ketogenic Diet for Mood Disorders, 48
OCD: Combination Therapy, 43
Peer Mentors and Rehospitalization, 45
Psychosis Conversion Model, 46
TMS for OCD, 43

September 2018

Adjunctive VNS in Depression, 51
Biological Aging and Depression, 52
Self-Injury: Online Self-Help, 51
Smartphone Apps for Mental Health, 53
Substance Abuse and Bipolar Recovery, 49
Suicide Risk Factors in Bipolar Disorder, 50

October 2018

CBT plus Biofeedback for PTSD, 58
Habenular Connectivity in Depression, 59
OCD: Concentrated Treatment, 55
rTMS in Pregnancy, 57
Traumatic Brain Injury and Suicide Risk, 56

November 2018

Cortisol and Depression/Anxiety Response, 64
Light Therapy for Depression, 64
Pharmacogenetic Test Approved, 63
Pharmacogenetic Testing Panel, 62
Virtual Reality Exposure for Anxiety, 65
VNS for Resistant Depression, 61

December 2018

Adult ADHD: Diagnosis Consensus, 71
Behavioral Addictions in Bipolar Disorder, 69
CBT App for Opioid Use Disorder, 69
Complementary Therapies in Pregnancy, 70
E-Prescribing: Warning Accuracy, 71
Functional Outcomes of High-Risk States, 68
Neurocognitive Therapy in Schizophrenia, 67

PSYCHIATRY ALERTS NOS

Alpha-Lipoic Acid in Schizophrenia	3
CBD in Schizophrenia	2
ECT for Dementia-Related Agitation	5
Internet-Based CBT for Bulimia.....	3
Reference Guide	6
Urine Screening Recommendations	1
Web-Based Treatment for Depression.....	4

Volume X / January 2018 / Number 1

www.alertpubs.com

You asked . . . We delivered. New Monthly CME . . . See back page for details.

Recommendations for Urine Testing

Urine testing for antipsychotic drugs can be extremely useful in monitoring medication adherence and identifying causes of clinical deterioration, according to an expert consensus of physicians working in community mental health clinics. Despite the inaccuracy of other methods (e.g., patient self-report, clinician estimates) to ascertain adherence in patients with serious mental illness, urine testing in mental health clinics remains uncommon. Urine testing technologies, available since 2013, can test simultaneously for illicit substances and levels of ingested medications, including antipsychotics. Results are available within a few days.

A literature search, focusing on recent articles and reviews, was conducted to identify research on antipsychotic medication. Semi-structured telephone interviews were also conducted with clinicians working in community mental health clinics that used urine drug testing. The interviews evaluated 46 "indications" or hypothetical scenarios, which were grouped into 5 areas: initial evaluation, urine monitoring method, education, feedback, and ongoing treatment. As a third step, a panel of the clinicians with considerable experience with testing rated each of the indications according to appropriateness; impact on treatment, symptoms, and functioning; and feasibility. Items with high ratings by consensus were included in the recommendations.

A total of 15 items, many consisting of combined indications, were highly rated for appropriateness, impact, and feasibility. Urine monitoring at initial intake is recommended for patients with: new symptoms; an established diagnosis of serious mental illness; a risk factor for poor adherence; homelessness; a substance use disorder; or advanced age. Written or verbal education prior to testing is critical and should include a discussion of the importance of adherence, the role of urine monitoring in treatment planning, and any costs the patient might incur. Results should be shared with the patient as soon as possible, and a clinician should be available to discuss concerns. Repeat testing is recommended if there were concerns about a previous result, the patient deteriorates or has an inadequate response,

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5625) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. Periodicals postage paid at Butler, NJ, and at additional mailing offices. Postmaster: Send address changes to Psychiatry Alerts NOS, 45 Carey Ave. Ste 111, Butler, NJ 07405. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Back issues and single copies are available for \$10.00 each, prepaid. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

or if there is a substantial change in the patient's situation that may require reevaluation. Periodic retesting is recommended, either at set intervals or randomly, and stable patients should be tested annually.

Cohen A, Collins G, Nucifora Jr F, Strobel R, et al: Clinical consensus recommendations for urine testing of adherence to antipsychotics among people with serious mental illness. *Psychiatric Services in Advance* 2017; doi 10.1176/appi.ps.201700082. From the University of California, Los Angeles; and other institutions. **Funded by Ameritox, Limited. All 6 study authors disclosed financial relationships with commercial sources including Ameritox.**

Adjunctive Cannabinoid for Schizophrenia

Cannabidiol (CBD), a non-intoxicating component of cannabis, reduced positive symptoms when added to background antipsychotic medication in patients with residual symptoms of schizophrenia. The effect was modest but of interest because CBD, unlike antipsychotics, does not appear to work via dopamine receptor antagonism.

Methods: The study was conducted at 15 hospital sites in 3 European countries by the British manufacturer of a CBD product. Participants were 88 adults (mean age, 41 years; 58% men) with a schizophrenia spectrum disorder, partially responsive to antipsychotic medication. Participants were required to have a Positive and Negative Syndrome Scale (PANSS) total score of ≥ 60 and to be receiving stable antipsychotic medication for ≥ 1 month. Substance use was not an exclusion criterion, and use of alcohol, marijuana, and other substances was not prohibited during the trial. Participants were randomly assigned to 6 weeks of double-blind treatment with 1000 mg/day CBD, administered in an oral solution in 2 split doses (morning and evening), or placebo. Because this was an exploratory study, there were multiple key efficacy endpoints and additional secondary endpoints.

Results: A total of 83 patients (94%) completed the trial. At baseline, the mean PANSS positive symptom scores were 18 and 17.5 in the CBD and placebo groups, respectively. At 6 weeks, scores were reduced to 14.8 with CBD and to 15.7 with placebo; although the difference was modest, it was statistically significant ($p=0.019$). Change in the other PANSS domains (i.e., total, negative, and general psychopathology) all favored CBD but fell short of statistical significance. Post-treatment Clinical Global Impression Improvement and Severity scores also differed between the groups. After treatment, more patients who received CBD were rated by their clinician as improved—79% vs 55% ($p=0.018$)—and the proportion of patients rated as having mild, borderline, or no illness was 45% in the CBD group and 36% in the placebo group ($p=0.044$). Differences between treatments in the level of functioning and cognitive performance favored CBD but were not statistically significant.

The treatment groups did not differ in prolactin levels, weight, abnormal movements, or any of the other known adverse effects of antipsychotics. Adverse events, mainly gastrointestinal, were generally transient and mild.

Discussion: Previous reports suggest CBD can reduce THC-induced psychosis as well as psychotic symptoms in schizophrenia and Parkinson's disease. Although the effects seen in the present study were modest, they were evident to the treating psychiatrists and were over and above the effects of patients' antipsychotic treatment.

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

McGuire P, Robson P, Cubala W, Vasile D, et al: Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multi-center randomized controlled trial. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.17030325. From King's College London, U.K.; and other institutions including GW Pharmaceuticals, Cambridge, U.K. **Funded by GW Research Ltd.; and other sources. Six study authors disclosed financial relationships with commercial sources including GW Pharmaceuticals; the remaining 2 authors declared no competing interests.**

*See Reference Guide.

Adjunctive Antioxidant for Schizophrenia

In a pilot study, adjunctive low-dose α -lipoic acid (ALA) reduced symptoms of schizophrenia in patients receiving stable antipsychotic medication. ALA is a naturally occurring antioxidant with antiinflammatory actions.

Methods: The trial enrolled 12 patients with chronic schizophrenia, receiving stable doses of antipsychotic medications for at least the previous year. All received 100 mg/day open-label ALA. Schizophrenia symptoms were evaluated using the Brief Psychiatric Rating Scale (BPRS) at baseline and after 4 months of treatment. Response was defined as a $\geq 25\%$ reduction in BPRS total score. Extrapyramidal symptoms were evaluated with the Simpson-Angus Scale at each monthly visit, and neurocognitive tests were given at entry and after 4 months.

Results: The 10 patients who completed the study had a mean age of 39 years and had been ill for an average of nearly 19 years. All 10 patients met response criteria, showing a mean 64% decrease in the BPRS total score. All symptom dimensions of the BPRS—positive, negative, excitement, and depressive—decreased significantly. Patients also showed improvement in all neurocognitive measures except for verbal fluency. Extrapyramidal symptoms also decreased in severity, and no adverse effects of ALA were observed. There were no changes from baseline in waist circumference, body mass index, complete blood count, or other laboratory variables. There were significant reductions in thiobarbituric acid-reactive substances (TBARS), a marker of lipid peroxidation, and in folic acid.

Discussion: Recent clinical studies, using dosages of 300 or 1200 mg/day, showed no benefit of ALA in patients with schizophrenia. However, older research suggested efficacy with lower dosages. The current findings, although preliminary and requiring replication, support the possibility of a low-dose therapeutic window for ALA in schizophrenia. Randomized trials are needed to confirm the efficacy of adjunctive ALA in schizophrenia.

Sanders L, de Souza Menezes C, Chaves Filho A, de Almeida Viana G, et al: α -Lipoic acid as adjunctive treatment for schizophrenia: an open-label trial. *Journal of Clinical Psychopharmacology* 2017;37 (December):697–701. From the Universidade Federal do Ceara, Brazil; and other institutions. **Funded by the Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil. The authors declared no competing interests.**

Internet-Based CBT for Bulimia

According to a randomized comparison study, after 1 year, efficacy and cost-effectiveness of internet-based cognitive behavioral therapy for bulimia nervosa are comparable to those of face-to-face therapy. However, over 1 year, out-of-pocket expenses were substantially higher for patients receiving face-to-face therapy.

Methods: A noninferiority trial, conducted at 2 U.S. centers, compared internet-based and face-to-face therapy for bulimia in 179 adults with DSM-IV bulimia nervosa. Both treatments were delivered in a group format, in 16 sessions (90 minutes each) over 20 weeks. Participants traveled to the study sites using personal transportation for face-to-face sessions. Internet therapy was conducted in a text-only online chat format, with anonymous logins and passwords. The primary effectiveness outcome was abstinence from binge eating and purging during the past 28 days, measured with the Eating Disorder Examination, at the end of treatment and at follow-up 1 year from the start of therapy. Cost items included the intervention itself; other health care outside the protocol; and out-of-pocket costs, including software for the internet group and travel time and expenses for face-to-face therapy.

Results: Patients in both groups participated in an average of 8 of the 16 sessions. About 40% completed $\geq 75\%$ of the sessions. Participants in face-to-face therapy had a higher rate of

binge-purge abstinence immediately after treatment (21% vs 14%), but by 1 year, similar proportions of the 2 groups were abstinent (26% and 30%, respectively). Overall costs of all protocol and non-protocol health care at 1 year were nearly identical for both programs, at slightly more than \$4000. However, patients' out-of-pocket expenses were >3-times higher in the face-to-face treatment group, primarily due to travel-related costs. There were no statistically significant differences in the calculated cost-effectiveness of the 2 treatments.

Discussion: Internet-based treatments are often assumed to cost less than face-to-face treatment, but these costs may not be accurately measured in most studies. The lack of difference in cost-effectiveness between internet and face-to-face CBT, along with the convenience and privacy of internet-delivered care, support internet-delivered CBT as a viable option for the treatment of bulimia. Although face-to-face therapy produced faster improvement, abstinence rates increased over time with internet therapy, perhaps because patients had access to online materials that they could continue to review. Accessibility of in-person CBT for bulimia is limited because it is generally provided only by specialized practitioners. Utilizing the internet-based therapy could improve access to care and/or reduce waiting lists for the specialized clinics.

Watson H, McLagan N, Zerwas S, Crosby R, et al: Cost-effectiveness of internet-based cognitive-behavioral treatment for bulimia nervosa: results of a randomized controlled trial. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.16m11314. From the University of North Carolina at Chapel Hill; and other institutions. **Funded by the NIH; and other sources. Six of 14 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Web-Based Adjunct to Psychotherapy for Depression

In a randomized trial, a web-based program was an effective adjunct to psychotherapy in patients with depression.

Methods: The program, called deprexis, was designed to provide some of the more routine aspects of therapy, mainly psychoeducation and cognitive-based homework. The program consists of 10 modules, covering such areas as cognitive restructuring, behavioral activation, exercise and nutrition, and emotion-focused interventions. Study participants were self-referred patients with unipolar depression and a Beck Depression Inventory-II (BDI-II) score >13. Treatment was provided by licensed therapists using their preferred mode of psychotherapy, with or without the randomly assigned addition of deprexis. All therapists were trained in the program and were free to monitor and support the study patients based on clinical judgment. The primary study outcome was change from baseline in BDI-II score after 12 weeks.

Results: A total of 98 patients were randomly assigned to treatment. More than half had a history of psychotherapy, and more than half were receiving stable antidepressant medication. A total of 69 patients (70%) completed the 12-week assessment, and 44 (45%) participated in follow-up at 6 months. Patients in the active treatment group used the program for >9 hours on average.

After 12 weeks, patients who used deprexis had a significantly greater improvement on the BDI-II than those who did not ($p < 0.05$; effect size, * 0.51). The difference was no longer statistically significant at 6 months (effect size, 0.28); however, <50% of patients completed this assessment. Statistically significant effects were also observed on some secondary outcomes: the mental health scale of the Short Form-12 (SF-12; effect size, 1.30; $p < 0.05$) and the somatic symptom module of the Patient Health Questionnaire-15 (effect size, 0.58; $p < 0.01$). The 2 groups did not differ on other secondary outcome measures, which included the physical subscale of the SF-12 and the Generalized Anxiety Disorder Scale. A total of 16

patients who received deprexis and 9 controls experienced reliable change from baseline in BDI-II score ($p=ns$); 8 and 2 patients, respectively, had clinically significant improvement on the BDI-II ($p=ns$). Generally, both clinicians and patients rated the working alliance higher if they received the web-based intervention, but differences were not statistically significant.

Discussion: Although preliminary, the present study results suggest that blending face-to-face psychotherapy with a web-based adjunctive intervention does not have negative effects on the quality of the therapeutic alliance, and that outcomes may actually improve as a result of participation in the online program. The authors note that the lower-than-anticipated sample size may have affected the study's ability to detect effects of more than medium magnitude, as well as potentially explain why significant differences were not detected on some secondary outcome measures.

Editor's Note: Additional information about the deprexis program is available from its developer, GAIA AG, at <https://us.deprexis.com>.

Berger T, Krieger T, Sude K, Meyer B, et al: Evaluating an e-mental health program ("deprexis") as an adjunctive treatment tool in psychotherapy for depression: results of a pragmatic randomized controlled trial. *Journal of Affective Disorders* 2018;227 (February):455–462. From the University of Bern, Switzerland; and other institutions. **Funded by the Swiss Natural Science Foundation. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

ECT for Dementia-Related Agitation, Aggression

According to a systematic review, ECT could produce clinically significant improvement in severe, resistant agitation and aggression in patients with dementia.

Methods: A comprehensive literature search identified reports of ECT for dementia-related behavior problems published in peer-reviewed journals, regardless of language or study design. Reviewed reports presented original data on patients who received ECT primarily to treat aggression or agitation; mood disorders were permitted but could not be the primary focus of treatment.

Results: The search identified 17 reports (122 patients; age range, 54–98 years), including 1 prospective cohort study with pre- and post-treatment comparisons and 1 case-control study. The remaining reports were retrospective chart reviews, case series, or single case reports. Although many aspects of the studies were not well documented (e.g., measures of cognitive function, concomitant medications, details of the ECT procedure), substantial clinical improvement was reported for 107 of the 122 patients (88%). Improvement often occurred after the second, third, or fourth session. Adverse effects of ECT were generally mild and transient. More severe adverse events were occasionally reported: delirium in 6 patients, seizure in 1, and severe postictal confusion in 2.

The only prospective study reported a statistically significant average improvement of 6 points each on the Cohen Mansfield Agitation Inventory and the Neuropsychiatric Inventory by the 6th ECT session. Most of the patients who improved were noticeably less agitated and aggressive, yelling and screaming stopped, and patients began eating again. Some patients continued to receive psychotropic medication to maintain their response, although at a reduced dose, and others were weaned. Of 82 initial responders for whom follow-up was described, 51 were referred for maintenance ECT.

Discussion: Based on the limited available evidence, ECT appears to be a viable option for treatment of resistant dementia-related agitation and aggression. However, controlled trials

are needed and it will be important to develop treatment guidelines, particularly because most patients who qualify will not be able to provide informed consent.

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

Van den Berg J, Kruithof H, Kok R, Verwijk E, et al: Electroconvulsive therapy for agitation and aggression in dementia: a systematic review. *American Journal of Geriatric Psychiatry* 2017; doi 10.1016/j.jagp.2017.09.023. From the Parnassia Psychiatric Institute, the Hague, the Netherlands; and other institutions. **Source of funding not stated. 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.

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.

YOU ASKED . . . WE DELIVERED

Our CME participants told us that they would like online exam modules to be released monthly rather than at the end of the issue cycle (every 6 months). We are happy to announce that beginning this month, we are adding more value and flexibility to the program by doing what you asked!

Participants in the online CME program will now be able complete each exam module shortly after the associated monthly issue is released. The modules will remain valid for the same length of time and can still be completed as a group at the end of the 6-month cycle. The traditional print program will not be affected by this change.

For additional details, or to enroll, call us at 973-898-1200
or visit www.alertpubs.com/continuing-education.html.

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**
Founding Editor: **Michael J. Powers**

Statement of Editorial Policy: All of the information and opinions presented in each Psychiatry Alerts NOS article are strictly those contained in the cited article unless otherwise noted. Reader comments are welcome by mail, by telephone, or by email.

PSYCHIATRY ALERTS NOS

Adaptive DBS for Tourette's	8
Botulinum Toxin for Depression	11
EMDR for Substance Use Disorder	10
E-Prescribing and Medication Errors.....	10
Reference Guide	12
Social Recovery Therapy for Psychosis.....	7
tDCS for Bipolar Depression.....	9

Volume X / February 2018 / Number 2

www.alertpubs.com

You asked . . . We delivered. New Monthly CME . . . See back page for details.

Social Recovery Therapy for First-Episode Psychosis

In a randomized trial, social recovery therapy was a useful addition to other intensive recovery-oriented services in highly impaired patients with first-episode psychosis.

Background: Social recovery therapy is a manualized treatment developed by the authors of this study to help first-episode patients who have continuing severe problems in social functioning. The therapy is delivered in 3 stages consisting of therapeutic engagement, assessment, and goal-setting; identifying pathways to meaningful new activities; and engagement in these activities. Other aspects of the treatment include referral to vocational, educational, and recreational resources in the community; behavioral experiments; assertive outreach with the patient at home or in the community; and work with family members, employers, and educators to address potential problems.

Methods: Study participants were aged 16–35 years, had a diagnosis of non-affective psychosis, and had been receiving early intervention services for 12–30 months. To be eligible for the study, participants were required to have low levels of structured activity, defined as ≤ 30 hours per week spent in activities as measured with the Time Use Survey. Subjects were randomly assigned to receive social recovery therapy in addition to their other specialized services or to receive the ongoing specialized services alone. Outcomes were assessed at 9 months (the end of treatment) and at 15 months by observers who were unaware of patients' treatment assignment. The primary efficacy outcome was change from baseline to the end of treatment in structured activity on the Time Use Survey, which measures economic activity (the sum of work, education, voluntary work, house work, and child care) and structured activity (economic activity plus leisure and sports). Secondary outcomes included measures of clinical symptoms.

Results: A total of 155 patients were randomized. Participants were predominantly men, single, and of white British ethnicity. At study entry, the mean total time spent in structured activity was 12 hours per week, compared with >60 hours for an age-matched healthy sample. Participants received a mean of 16.5 sessions of social recovery therapy, and 61 patients (81%) in the therapy group received what was considered an adequate dose of treatment.

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5625) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. Periodicals postage paid at Butler, NJ, and at additional mailing offices. Postmaster: Send address changes to Psychiatry Alerts NOS, 45 Carey Ave. Ste 111, Butler, NJ 07405. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Back issues and single copies are available for \$10.00 each, prepaid. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

The program resulted in a clinically important gain in time spent in structured activity by the end of treatment: an average of 8.1 hours compared with early intervention services alone ($p=0.005$). This increase is double the minimum clinically important difference of 4 hours that was estimated by a consensus group before the study. Constructive economic activity increased by a mean of 6.2 hours at 9 months, relative to the control group ($p=0.02$). Secondary outcomes, including scores on the Positive and Negative Syndrome Scale and Schedule for the Assessment of Negative Symptoms, also showed improvement with social recovery therapy, but the between-group differences were not statistically significant, possibly because attrition rates were high and missing evaluations were common in the placebo group.

Discussion: Adding social recovery therapy appears to improve functional outcomes in people with first-episode psychosis. It may be particularly useful for those not motivated to engage in existing psychosocial interventions targeting functioning, or for those who have comorbid difficulties that prevent them from doing so.

Fowler D, Hodgekins J, French P, Marshall M, et al: Social recovery therapy in combination with early intervention services for enhancement of social recovery in patients with first-episode psychosis (SUPEREDEN3): a single-blind, randomised controlled trial. *Lancet Psychiatry* 2018;5 (January):41–50. From the University of Sussex, Brighton, U.K.; and other institutions. **Funded by the National Institute for Health Research. The authors declared no competing interests.**

Adaptive Deep Brain Stimulation for Tourette Syndrome

According to the results of several small clinical experiments in patients with severe Tourette syndrome along with a literature review, adaptive deep brain stimulation (aDBS) appears to be a promising treatment for patients with refractory disease.

Conventional DBS is gaining favor as a treatment in refractory Tourette syndrome. However, the continuous operation of conventional DBS devices contributes to adverse effects and leads to rapid battery depletion and frequent battery-replacement surgeries. The only alternative to continuous DBS studied thus far is intermittent DBS, with the device switched on for a few hours each day. In contrast, aDBS uses a closed-loop system that measures and analyzes a control variable reflecting the patient's clinical status. Stimulation settings are modified based on the readings in order to control the patient's symptoms. This results in a new control variable, which is then measured and analyzed again, thus closing the loop. Local field potentials (LFPs) are sums of pre- and post-synaptic activity directly recorded from the implanted DBS electrodes. These can function as a marker for tics and can be used to modify DBS parameters in response. When the LFPs return to their background state, the DBS device can revert to its usual settings.

aDBS has been extensively investigated in Parkinson's disease. The present report describes LFP recordings at rest and during both voluntary and involuntary movement in 7 patients with severe Tourette syndrome. The recordings showed activity patterns suggestive of increased firing of thalamic cells in the low-frequency range. Chronic LFP patterns were also observed in 8 patients who returned to the clinic for battery replacement after 1–7 years of DBS treatment. Circumstances limited the observations to at-rest, with the DBS device turned on or off but with no voluntary movement or tic activity. aDBS was shown to modulate LFP patterns only by increasing low-frequency activity. When the device was switched off, low-frequency activity returned to baseline levels. These findings suggest that changes in low-frequency and alpha-band activity can be used to trigger changes in DBS parameters that would reduce or suppress this activity, hypothetically preventing tic onset.

Marceglia S, Rosa M, Servello D, Porta M, et al: Adaptive deep brain stimulation (aDBS) for Tourette syndrome. *Brain Science* 2018; doi 10.3390/brainsci8010004. From the Ospedale Maggiore Policlinico, Milan, Italy; and other institutions. **Funded by the European Research Area Networks Neuron Project; and other sources. Four of 7 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.** See related story in *Psychiatry Alerts NOS* 2017;9 (November):62–63.

Direct Current Brain Stimulation for Bipolar Depression

In a randomized, sham-controlled trial, adjunctive transcranial direct current stimulation (tDCS) was associated with improvement in bipolar depression. The treatment did not appear to induce mania or hypomania.

Methods: Study participants were adults with bipolar I or II disorder, currently experiencing a depressive episode, with a Hamilton Rating Scale for Depression (HAM-D) score of >17. Participants were included only if their depression had previously not responded to ≥1 antidepressant treatment, in addition to ongoing mood-stabilizer therapy. Anxiety disorders were the only permitted psychiatric comorbidity. Participants were randomly assigned to receive real or sham tDCS. The anode and cathode electrodes were placed over the left and right dorsolateral prefrontal cortex, respectively. Each of the active sessions consisted of 30 minutes of 12 2-mA stimulations. Patients received 10 treatments on consecutive weekdays, followed by 1 session at week 4 and another at week 6. The primary study outcome was change from baseline in HAM-D score at week 6. Secondary outcome measures included the Montgomery-Asberg Depression Rating Scale (MADRS) and the Young Mania Rating Scale.

Results: A total of 59 patients were enrolled, and 52 completed all tDCS sessions. About two-thirds of patients had bipolar I disorder. About half had severe depression, and 86% had a concomitant anxiety disorder. One third met formal criteria for treatment-resistant depression. Patients had taken a mean of 1.3 antidepressants in the current episode, and three fourths were taking antidepressant medication at the start of the trial.

In the intent-to treat analysis, patients who received active tDCS had significantly larger reductions in depressive symptoms than those who received sham treatment ($p=0.01$; see table). Sustained response (HAM-D decrease of >50%, lasting until the end of the study) occurred in 19 actively treated patients, compared with 8 controls (68% vs 30%; hazard ratio,* 2.86; $p=0.01$). Sustained remission (HAM-D ≤7) was achieved by 10 patients in the active tDCS group and by 5 in the control group (37% vs 19%; $p=ns$). Skin redness occurred after treatment in higher proportions of active versus sham tDCS groups. Despite this, blinding was preserved, and <60% of patients correctly identified their treatment. The frequency of other adverse effects did not differ between groups. There were no episodes of emergent mixed features, mania, or hypomania.

Depressive Symptom Measures Over 6 Weeks with Active vs Sham tDCS					
	Treatment group	Baseline	Week 2	Week 4	Week 6
HAM-D	Active	23.1	11.4	10.7	10.3
	Sham	23.5	15.8	14.7	16.2
MADRS	Active	28.7	15.1	14.2	13.6
	Sham	27.9	19.5	18.3	19

Discussion: This appears to be the first sham-controlled trial of tDCS in a purely bipolar patient population. As a result, although positive, the findings should be viewed as preliminary.

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

Sampaio-Junior B, Tortella G, Borrión L, Moffa A, et al: Efficacy and safety of transcranial direct current stimulation as an add-on treatment for bipolar depression: a randomized clinical trial. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.2040. From the University of Sao Paulo, Brazil; and other institutions. **Funded by the Brain and Behavior Research Foundation; and other sources. Two of 16 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

*See Reference Guide.

E-Prescribing and Medication Errors

The effects of e-prescribing on medication errors in outpatient psychiatry have not been evaluated, but preliminary evidence from inpatient psychiatry and other areas of medicine suggest some types of errors are reduced drastically. Nonetheless, e-prescribing has created the potential for some new types of error, according to a review.

In outpatient psychiatry, medication errors have the potential to not only harm patients directly, but could also jeopardize the clinician–patient alliance. The integration of e-prescribing into clinical practice was anticipated to drastically reduce errors from illegible handwriting, lost prescription slips, and incomplete/inaccurate instructions. Government incentive programs within Medicare have dramatically increased rates of e-prescribing and reduced the rates of these types of error. However, potential for error still exists because e-prescribing does not fully prevent the omission of the dose or strength, prescribing the wrong medication, failing to discontinue a prescription, or prescribing the same medication multiple times. Accuracy may suffer from too many distracting on-screen alerts and from the loss of interaction between prescriber and pharmacist. Internet-based refill systems may contain duplicate or outdated prescriptions. Pharmacists may still have difficulty communicating to clarify prescriptions.

E-prescribing systems could simplify medication reconciliation by matching what the patient is taking to what is in the record. Because patients often use multiple clinicians and multiple pharmacies, interoperability between the related prescribing systems should be improved. However, increased interoperability may reveal too much sensitive information to nonpsychiatric providers and may be perceived as an invasion of the patient's privacy. Systems should allow for real-time chat between pharmacists and prescribers. Most e-prescribing systems do not allow for prescription of controlled substances such as stimulants and benzodiazepines, which are commonly used in psychiatry. However, linking an e-prescribing system to a state's monitoring program for controlled substances poses difficulties. Finally, implementing e-prescribing in small-group and solo practices, where a large portion of psychiatric care takes place, would be costly. Including financial incentives or assistance in state or federal mandates could improve accessibility to e-prescribing platforms.

Hirschtritt M, Chan S, Ly W: Realizing e-prescribing's potential to reduce outpatient psychiatric medication errors. *Psychiatric Services* 2018;69 (February):129–132. From the University of California, San Francisco. **Funded by the NIMH; and other sources. One study author disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

EMDR in Substance Use Disorder

In a preliminary study, eye movement desensitization and reprocessing improved post-traumatic, dissociative, and general psychiatric symptoms in patients with substance use disorder.

Background: Several lines of evidence suggest a role for childhood trauma, stress-related brain systems, and PTSD in substance use disorder. Originally developed for treating psychological sequelae of traumatic events, EMDR is now used to treat trauma-associated symptoms in other psychiatric disorders. Addiction-focused EMDR has had promising results in substance use disorders, but no studies as yet have evaluated the efficacy of combined trauma-focused and addiction-focused EMDR.

Methods: Study participants were 40 adults with a DSM-5 diagnosis of substance use disorder who had been referred for addiction treatment. Patients could choose whether or not to receive EMDR as an add-on to treatment as usual (TAU). When the 20 available EMDR slots were filled, all remaining patients were assigned to TAU. EMDR was delivered in 24 weekly sessions by

specialized clinical psychotherapists and incorporated elements of both the classic trauma-focused protocol and addiction-focused EMDR. TAU included clinical specialist interviews, medication, group and individual psychology, psychoeducation, and treatment of comorbid psychiatric conditions.

Results: All enrolled patients completed treatment. The 2 groups were demographically similar at baseline, with a mean age of 32 years and an average of about 20 years of substance use. Patients who chose EMDR reported a significantly higher average number of adverse childhood experiences as well as higher baseline levels of post-traumatic stress and anxiety symptoms and more comorbid psychiatric symptoms.

Over time, both groups showed statistically significant improvement in dissociative and psychiatric symptoms, measured using standardized scales. Improvements were larger in the EMDR group, so that at the end of treatment, there were few significant between-group differences in symptom measures despite significantly higher baseline levels in the EMDR group. Depressive symptoms were not significantly improved in either treatment group. Anxiety, which often accompanies abstinence from substance use, worsened in the TAU group for both state and trait measures. In contrast, the EMDR group experienced significant reductions from baseline in trait anxiety and a trend-level improvement that did not reach significance in state anxiety. At endpoint, there were no significant differences between the groups in levels of anxiety, again despite significantly higher baseline levels in the EMDR group. There were no differences between the groups in the proportion of negative urine drug assays after treatment.

Discussion: All study participants showed clinical improvement in anxiety and dissociative and psychiatric symptoms, regardless of the type of treatment. However, the effects were stronger in patients who received EMDR. Although preliminary and requiring replication, these results suggest that EMDR may be useful in the treatment of substance abuse disorders particularly in patients with more adverse childhood experiences and higher levels of symptoms.

Carletto S, Oliva F, Barnato M, Antonelli T, et al: EMDR as add-on treatment for psychiatric and traumatic symptoms in patients with substance use disorder. *Frontiers in Psychology* 2018; doi 10.3389/fpsyg.2017.02333. From the University of Turin, Orbassano, Italy; and other institutions. **Source of funding not stated. Four of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Botulinum Toxin for Depression

Results of early clinical trials and meta-analyses have suggested that a single treatment with onabotulinumtoxinA (BTX; *Botox*) to glabellar frown lines can improve depressive symptoms in women. According to the present large consecutive case series, BTX is also effective in men and in individuals with severe, resistant depression.

Methods: Records were reviewed for 42 patients who received treatment at 2 private specialty practices in India. All patients had severe depression without psychotic features, either single-episode or recurrent. In all cases, the present episode of depression was refractory to 4–6-week courses of ≥ 2 different antidepressants at labeled dosages. All of the patients had glabellar frown lines, which were severe in most according to standardized criteria. All patients received a single treatment consisting of injections of BTX at 5 specific sites on the forehead according to the approved cosmetic indication, as an adjunct to antidepressant medication that had been stable for ≥ 6 weeks. Depression severity was measured before and 3 weeks after BTX injection using the 17-item Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Beck Depression Inventory (BDI). Patients were observed clinically for ≥ 6 additional weeks, although psychometric depression scales were not administered during that time.

Results: The patients (23 men, 19 women) did not differ from each other in average age (about 45 years), duration of the current depressive episode (about 8 months), or baseline depression severity. On average, patients experienced a nearly 30% decrease in symptoms over the 3 weeks post injection. Mean HAM-D scores decreased from 33 at baseline to 24 after 3 weeks, mean MADRS scores decreased from 48 to 35, and mean BDI scores decreased from 46 to 34 ($p < 0.0001$ for all). All but 1 patient experienced what was considered a clinically meaningful improvement in depression symptoms, and 57% experienced partial response, defined as a $\geq 25\%$ reduction in HAM-D score. However, at 3 weeks, depressive symptoms remained in the moderate to severe range despite the improvement occurring with BTX injection. Treatment effects did not differ between women and men. Improvement in frown-line severity showed a weak positive correlation with improvement on the HAM-D (correlation coefficient, $* 0.37$; $p < 0.05$). During additional follow-up, all patients reported continued improvement in their depressive symptoms, with no further change in their treatment.

Discussion: The study results suggest BTX injection may produce early improvement in depressive symptoms, which has consistently been shown to predict later response and remission. In resource-rich environments, patients with severe depression would likely receive multimodal treatment; however, this level of care may not be available to all patients. BTX injection, because it requires limited aftercare, may be a viable option for treatment-resistant depression in more limited domains.

Chugh S, Chhabria A, Jung S, Kruger T, et al: Botulinum toxin as a treatment for depression in a real-world setting. *Journal of Psychiatric Practice* 2018;24 (January):15–20. From private practice, New Delhi, India; and other institutions. This study was conducted without outside funding. Two of 5 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests. See related stories in *Psychiatry Alerts* NOS 2012;4 (March):14–15; 2014;6 (May):27; and 2015;7 (October):58–59.

*See Reference Guide.

Reference Guide

Correlation Coefficient (r): A measure of the closeness of the relationship between 2 variables. The value of r can range from -1 to 1. An r value near 1 indicates a strong positive relationship. An r-value close to zero indicates no relationship, and a negative r-value indicates a negative relationship.

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.

YOU ASKED . . . WE DELIVERED

You told us you wanted to complete online exam modules monthly rather than at the end of the issue cycle (every 6 months). We are happy to announce that beginning with the current test, you can do just that! Online modules will now be released shortly after the monthly issued is published.

For additional details, or to enroll, call us at 973-898-1200 or visit www.alertpubs.com.

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**
Founding Editor: **Michael J. Powers**

PSYCHIATRY ALERTS NOS

Behavioral Avoidance in OCD.....	16
Brain Stimulation for Substance Use Disorders.....	13
Computer-Assisted CBT for Depression.....	15
Inflammatory Marker and ECT Response.....	17
Reference Guide	18
Virtual Reality Treatment for Paranoia	15
VNS: Long-Term Effects on Depression	14

Volume X / March 2018 / Number 3

www.alertpubs.com

You asked . . . We delivered. New Monthly CME . . . See back page for details.

Brain Stimulation for Substance Use Disorders

Preliminary evidence indicates that brain stimulation techniques may be a promising approach for substance use disorders.

Methods: A comprehensive literature search was undertaken to identify studies of repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS) in the treatment of alcohol, tobacco, cocaine, methamphetamine, opioid, and cannabis use disorders. The present review includes only studies whose participants met criteria for DSM-IV substance abuse or dependence or DSM-5 substance use disorders and whose primary or secondary outcomes were related to substance use (e.g., craving, consumption, or abstinence) or drug cue-induced functional imaging changes. A total of 60 studies met criteria; most were preliminary and had sample sizes <40.

Results: rTMS has demonstrated positive effects on craving and consumption in patients dependent on alcohol, nicotine, and cocaine. Effects in methamphetamine dependence have been mixed, and rTMS does not appear to improve cannabis dependence. Studies have shown the effects of tDCS are generally positive in substance use disorders. The treatment reduced cravings and consumption in alcohol, tobacco, cocaine, methamphetamine, opioid, and cannabis dependence. All DBS studies in alcohol, tobacco, cocaine, and opioid use disorders demonstrated positive effects.

Variations in stimulation parameters, differences among the disorders, and heterogeneity in the populations studied, including the presence of comorbid psychiatric disorders in some, appear to impact the efficacy of all 3 neuromodulation techniques in substance use disorders. Effect sizes* were promising but highly variable and were similar for rTMS and tDCS, ranging from small negative effects to very large effect sizes as high as 4. Both of these techniques were more effective when used repeatedly, and tDCS when it was applied for >10 minutes. High-frequency rTMS seems to be more effective than low-frequency. In most studies, both of these techniques were targeted to the dorsolateral prefrontal cortex (DLPFC). Specifically targeting the right DLPFC was more effective than the left. All DBS studies targeted the nucleus accumbens.

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5625) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. Periodicals postage paid at Butler, NJ, and at additional mailing offices. Postmaster: Send address changes to Psychiatry Alerts NOS, 45 Carey Ave. Ste 111, Butler, NJ 07405. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Back issues and single copies are available for \$10.00 each, prepaid. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

Discussion: While these results suggest neuromodulation may be helpful for patients with substance use disorders, few of the studies followed patients long-term, there were no within-study comparisons of different brain regions or stimulation parameters, and the evidence base includes only a few studies of each treatment modality in each disorder. In spite of the limitations highlighted by this overview, additional study of neuromodulation in substance use disorders appears to be warranted. However, it should be noted that in order to produce improvement, stimulation should target brain regions relating to the reward pathway to reduce craving and consumption.

Coles A, Kozak K, George T: A review of brain stimulation methods to treat substance use disorders. *American Journal on Addictions* 2018; doi 10.1111/ajad.12674. From the Centre for Addiction and Mental Health, Toronto; and the University of Toronto, Canada. **Funded by the Canadian Institutes of Health Research; and other sources. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

VNS: Long-Term Effects on Depression

Results of a small, 6-year, naturalistic follow-up study of patients with treatment-resistant depression suggest that vagus nerve stimulation produces lasting improvements in depressive symptoms and quality of life.

Methods: Study subjects (n=10; 6 women) had a diagnosis of major depression that had been resistant to ≥ 3 antidepressant trials. All patients began receiving VNS at the University of Montreal between November 2007 and April 2010 and were followed for 72 months. Patients' background treatments were continued throughout the study period, but no changes were permitted during the first year of VNS therapy. At baseline and 9 follow-up points, depression and anxiety symptoms were evaluated using the Hamilton Rating Scales for Depression and Anxiety (HAM-D and HAM-A, respectively), and quality of life (mental and physical) was assessed using the 36-item Short Form Survey. Treatment response was defined as a $\geq 50\%$ decrease in HAM-D score, and remission as a final score of ≤ 7 .

Results: All 10 patients completed the full 6 years of follow-up assessments. Clinically and statistically significant improvement in depression was evident throughout the study, beginning at the 1-month evaluation. The mean HAM-D score decreased from 27 at baseline to 16 at 1 month ($p=0.001$), and then continued to decline, reaching a final mean of 8 at 72 months ($p<0.001$). Response was achieved by 30% of patients at 1 month, by 70% of patients at 12 months, and by 80% of patients at 72 months. Remission rates were 30% at 1 month and 50% at both the 12- and 72-month evaluations. Reductions in anxiety showed a similar pattern. HAM-A scores decreased from 16 at baseline to 10 at 1 month and reached a final mean of 6 at 72 months ($p<0.001$). Quality of life also improved significantly in patients treated with VNS, although the magnitude of improvement was substantially larger on the mental-health versus the physical-health component.

Discussion: While the small cohort of subjects is an important limitation, these study results appear to be the first indicating that VNS produces sustained improvement in symptoms as well as quality of life for as long as 6 years. Clinical improvement occurred earlier in these patients than has been previously reported in VNS studies, but overall response and remission rates were similar to previous reports. The authors note that the rate of remission with VNS in these patients was higher than that generally reported for repetitive transcranial magnetic stimulation and only slightly lower than that reported for ECT.

Trottier-Duclos F, Jodoin V, Fournier-Gosselin M, Richer F, et al: A 6-year follow-up study of vagus nerve stimulation effect on quality of life in treatment-resistant depression: a pilot study. *Journal of ECT* 2018; doi 10.1097/YCT.0000000000000485. From Centre Hospitalier Universitaire de Montreal; and Universite du Quebec a Montreal, Canada. **Source of funding not stated. Two of 7 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Virtual Reality Treatment for Paranoia

As an add-on to standard treatment, virtual-reality-based cognitive behavioral therapy (VR-CBT) led to reduced paranoid ideation and momentary anxiety in patients with psychosis. The treatment also modestly reduced safety behaviors, which could potentially lead to long-term improvement in social interactions.

Methods: Study participants (n=116) were adult outpatients with a psychotic disorder who were experiencing paranoid ideation with avoidance of various public places. All participants received standard treatment, and half were randomly assigned to undergo additional, single-blind VR-CBT. The virtual-reality intervention was designed to avoid some of the limitations of standard exposure-based CBT exercises for paranoid ideation by providing therapist control of the social environment, allowing real-time feedback, and overcoming patients' fears and negative symptoms. The treatment was delivered in virtual environments (e.g., a street or cafe) populated by therapist-operated avatars whose characteristics and behavior were tailored to match the paranoid fears of the patient. Each of the 16 planned sessions consisted of 40 minutes of virtual reality and 20 minutes of discussion and planning. No homework exercises were assigned. The primary outcome was social participation, measured by blinded raters using 4 constructs: amount of time spent with others, momentary paranoia, perceived social threat, and momentary anxiety in company.

Results: At the end of 3 months of treatment, patients in the virtual-reality group had large reductions in momentary paranoia and anxiety, compared with the control group ($p < 0.0001$), effects that remained significant at 6-month follow-up ($p \leq 0.007$). Treatment had no acute effects on time spent with others. However, at follow-up, time spent with others decreased somewhat in the control group but was unchanged in the VR-CBT group. Treatment had a small positive effect on perceived social threat. Use of safety behaviors (e.g., avoiding eye contact) decreased significantly in the virtual reality group at 3 and 6 months. The treatment was also associated with reduced ideas of persecution, social reference, and self-stigmatization and with improved social functioning. The treatment effect on paranoid ideation was mediated by change in safety behavior (34%) and social cognitive problems (19%). Quality of life did not differ significantly between the groups. The only reported adverse effect of VR-CBT was cybersickness (i.e., visual motion sickness), which caused 1 patient to withdraw from the study.

Discussion: The lack of a treatment effect on time spent with others was an unexpected result. The authors suggest that safety behaviors interfere with gathering social information and forming new associations, and the effects of treatment may not be immediate.

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

Pot-Kolder R, Geraets C, Veling W, van Beilen M, et al: Virtual-reality-based cognitive behavioural therapy versus waiting list control for paranoid ideation and social avoidance in patients with psychotic disorders: a single-blind randomised controlled trial. *Lancet Psychiatry* 2018; doi 10.1016/S2215-0366(18)30053-1. From VU University, Amsterdam; and Amsterdam Public Health Research Institute, the Netherlands; and other institutions. **Funded by Fonds NutsOhra, Stichting tot Steun VCVGZ. The authors declared no competing interests.**

*See Reference Guide.

Computer-Assisted CBT for Depression

In a randomized comparison, efficacy and acceptability of computer-assisted cognitive behavioral therapy (CCBT) were similar to standard CBT in patients with major depression, despite using one-third the therapist hours.¹

Methods: This noninferiority study was conducted at 1 institution that had developed a standard CBT program (University of Pennsylvania) and another institution that had implemented

the Good Days Ahead computer-assisted CBT program (University of Louisville). The study was designed to minimize potential allegiance bias by distributing both types of therapy between therapists at both institutions. Study subjects were patients who met DSM-IV criteria for major depression and did not have psychosis, bipolar disorder, or alcohol or drug dependence. Participants were required to discontinue any previous antidepressant medication. Standard CBT was delivered in up to 20 sessions (50 minutes each) over 16 weeks, with up to 1000 minutes of therapist time. Therapists delivering CCBT provided up to 325 minutes of patient contact in 25-minute sessions distributed over 16 weeks. The internet-based component included 9 self-study modules covering the standard elements of CBT. The primary study outcome measure was the Hamilton Rating Scale for Depression (HAM-D), with a 4-point difference between the groups demonstrating noninferiority. Outcomes were assessed upon treatment completion and then 3 and 6 months later.

Results: A total of 154 patients were randomly assigned to CBT or CCBT. About 80% of patients in both groups completed treatment. Patients in the CBT group received a mean of 13.3 hours of therapist time, compared with 5 hours for the CCBT group. At study entry, depression severity was moderate as indicated by an average baseline HAM-D score of about 20.

At week 16, mean HAM-D scores were 9.2 in the CBT group and 8.9 in the CCBT group, well below the noninferiority threshold (between-group effect size,* 0.05). Both groups experienced marked improvement during treatment, with within-group effect sizes of 2.4 and 2.0 for CCBT and CBT, respectively. Remission rates were 43% and 42%, respectively. The results of treatment did not differ between the study sites, which indicates investigator allegiance and differences in familiarity with CCBT did not influence the results.

Treatment effects were maintained at the 3- and 6-month evaluations, with no differences between groups in measures of symptoms or function. Patients who received CCBT finished the program with a higher level of knowledge about the methods of CBT, which they retained throughout follow-up. Among the 55 participants who remitted and remained in follow-up, there were 2 relapses in the CBT group and 4 in the CCBT group.

Discussion: Previous studies of CCBT have generally compared it with treatment-as-usual or with an inactive control condition. A few small studies have compared CCBT with standard CBT, with similar results to those of the present, relatively large study. Although well designed, the present study had important limitations, according to both the authors and an accompanying editorial.² Because it delivers a reduced "dose" of therapist time, CCBT may not be appropriate for patients with more severe or longstanding depression or those with comorbidity.

¹Thase M, Wright J, Eells T, Barrett M, et al: Improving the efficiency of psychotherapy for depression: computer-assisted versus standard CBT. *American Journal of Psychiatry* 2018;175 (March):242–250. From the University of Pennsylvania, Philadelphia; and other institutions. **Funded by the NIMH. Two of 8 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

²Kocsis J: Internet-based psychotherapy: How far can we go [editorial]? *American Journal of Psychiatry* 2018;175 (March):202–203. From New York-Presbyterian Hospital and Weill Cornell Medicine, New York, NY. **The author declared no competing interests.**

*See Reference Guide.

Behavioral Avoidance and OCD Outcomes

Moderate-to-high baseline levels of avoidance predict a poorer response to exposure and response prevention (ERP) therapy for obsessive-compulsive disorder, according to a post-hoc analysis of a clinical trial. Measuring avoidance, which can be done using an auxiliary item on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), could help clinicians identify patients who might benefit from additional clinical support in completing exposure assignments.

Methods: The randomized trial enrolled 100 adults with OCD who remained symptomatic despite ≥ 12 weeks of SRI therapy. Patients were randomly assigned to augmentation of ongoing medication with ERP, an atypical antipsychotic, or placebo. ERP consisted of 2 planning sessions plus 15 sessions with exposures (90 min each), in addition to between-session self-directed exposure homework. Avoidance was measured at baseline with a Y-BOCS auxiliary item in which raters ask the patient to estimate, on a scale of 1–4, the extent to which they avoid places, situations, or people because of obsessional thoughts or the need to perform compulsions. For the present analysis, the ratings were grouped as none/mild and moderate/extreme. Adherence to ERP was measured with the Patient EX/RP Adherence Scale (PEAS), which rates the quantity and quality of exposures and the degree of success of response prevention. The primary outcome of the clinical trial was change from baseline in the Y-BOCS. Effects of baseline avoidance were analyzed separately for each treatment group.

Results: Of the 40 patients who received ERP, 37 completed treatment. The mean Y-BOCS score decreased after ERP, from 27 to 13 ($p < 0.001$). Avoidance was moderately and negatively correlated with PEAS scores (correlation coefficient,* -0.49 ; $p = 0.002$), indicating that patients with significant avoidance were less adherent to ERP procedures.

Pretreatment Y-BOCS scores were not predictive of posttreatment scores. Moderate-to-high levels of pretreatment avoidance were significantly associated with posttreatment scores ($p = 0.01$) in the ERP group. Pretreatment avoidance did not predict the outcome of drug or placebo treatment. Patients with high baseline avoidance were less likely to achieve wellness (defined as a Y-BOCS score ≤ 12) than those with lower avoidance scores. The relationship between high baseline avoidance and poor outcome was mediated by poor adherence, which accounted for nearly 50% of the relationship.

Discussion: Although ERP is effective in OCD, fewer than half of patients achieve minimal symptoms. Assessing baseline avoidance could help clinicians identify patients at risk for poor treatment adherence and suboptimal ERP outcomes.

Wheaton M, Gershkovich M, Gallagher T, Foa E, et al: Behavioral avoidance predicts treatment outcome with exposure and response prevention for obsessive-compulsive disorder. *Depression and Anxiety* 2018; doi 10.1002/da.22720. From Barnard College, New York, NY; and other institutions. **Funded by the NIMH; and the New York State Office of Mental Hygiene. Two of 5 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

*See Reference Guide.

Inflammatory Marker and ECT Response

Levels of the inflammatory marker interleukin 6 (IL-6) were predictive of response to ECT in patients with treatment-resistant depression, particularly in women. This finding supports the concept of an "inflammatory subtype" of depression that is associated with female gender and that may respond poorly to antidepressant medications.

Methods: Inflammatory markers were measured in 29 patients (15 women) scheduled to undergo ECT. Patients were experiencing a current major depressive episode, had ≥ 2 prior episodes, and had experienced nonresponse to ≥ 2 antidepressants. They received ECT 3 times a week for a total of 6–22 sessions. Inflammatory cytokines—IL-1beta, IL-6, IL-8, and TNF-alpha—and C-reactive protein (CRP) were measured in blood samples obtained at baseline, between the second and third ECT treatments, and within a week after completing the series. Depressive symptoms were measured using the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: The mean MADRS score decreased from 40 at baseline to 31 at the end of treatment ($p < 0.001$). Mean levels of IL-6 nearly tripled, and CRP increased by a factor of 5.5 after the first ECT exposures and returned to previous levels by the end of treatment.

Higher baseline levels of IL-6 predicted larger reductions in the MADRS at the end of treatment. The relationship was stronger in women than in men ($p=0.02$ and $p=0.10$, respectively). Baseline CRP also predicted response in women ($p=0.04$), but not in men. Baseline levels of inflammatory markers did not differ between the sexes. Improvement on the MADRS was not associated with pretreatment levels of the other markers or with changes over time in any of the markers.

Discussion: This finding, if replicated, suggests inflammatory markers could help identify patients who might be prioritized for advancement to ECT. The association of baseline IL-6 with clinical outcome was independent of other clinical variables such as age, symptom severity, and duration of the current illness episode. Previous research has shown cytokines become elevated after a single ECT session but then return to previous levels. These transient elevations may represent acute stress-induced inflammation and do not affect clinical outcome.

Kruse J, Congdon E, Olmstead R, Njau S, et al: Inflammation and improvement of depression following electroconvulsive therapy in treatment-resistant depression. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11597. From the University of California at Los Angeles. **Funded by the NIH. The authors declared no competing interests.**

Reference Guide

Correlation Coefficient (r): A measure of the closeness of the relationship between 2 variables. The value of r can range from -1 to 1 . An r value near 1 indicates a strong positive relationship. An r -value close to zero indicates no relationship, and a negative r -value indicates a negative relationship.

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

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

YOU ASKED . . . WE DELIVERED

You told us you wanted to complete online exam modules monthly rather than at the end of the issue cycle (every 6 months). We are happy to announce that you can now do just that! Online modules will now be released shortly after the monthly issue is published.

**For additional details, or to enroll, call us at 973-898-1200
or visit www.alertpubs.com.**

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**
Founding Editor: **Michael J. Powers**

PSYCHIATRY ALERTS NOS

Aggression and Creatine Kinase Levels	22
Bipolar Conversion Predictors	19
CET plus tDCS for Resistant Depression	23
Depression Relapse and Brain Morphology	21
Mental Health Apps: Evaluation	20
Reference Guide	24
Schizophrenia: Gene Mapping.....	23

Volume X / April 2018 / Number 4

www.alertpubs.com

You asked . . . We delivered. New Monthly CME . . . See back page for details.

Predicting Bipolar Conversion

According to the results of a cohort study, the strongest predictor of conversion from unipolar depression to bipolar depression is a parental history of bipolar disorder. Other significant predictors include psychotic depression at the index episode, emergency or inpatient treatment of the index episode, and prior or concurrent nonaffective psychosis.

Background: The occurrence of the first episode of hypomania, mania, or mixed symptoms in a patient with depression signals conversion to bipolar disorder and should prompt modifications in treatment. However, detection of this conversion is often clinically delayed and results in long periods of untreated bipolar disorder, which are known to negatively affect outcomes. The current historical prospective cohort study was undertaken to confirm previously identified risk factors in a large representative patient sample.

Methods: Using data from linked Danish civil and psychiatric registries, a cohort of >91,000 patients with a first diagnosis of unipolar major depression between 1995 and 2016 were identified. Conversion to a diagnosis of bipolar depression during the follow-up period, which began 8 weeks after the index episode, was the primary outcome. Based on previous research, the following clinical predictors for conversion were evaluated: gender; age at onset; treatment setting of the index depressive episode; characteristics of the index episode (i.e., severity, presence of psychotic symptoms, recurrent vs single episode); concomitant mental health diagnoses; and parental mental health disorders.

Results: The study cohort (n=91,587) had a mean age of 31 years at the index depressive episode, and 63% of patients were female. Most (57%) received treatment as outpatients, and nearly 40% had a concomitant psychiatric diagnosis. Parental history of psychiatric disorder was present in 27% of the cohort. The mean duration of follow-up was 8 years.

During follow-up, a total of 3910 patients experienced conversion to bipolar depression, making the overall cumulative incidence of conversion 8.4%. Risk was greatest during the first year after unipolar depression diagnosis. The strongest predictor of conversion was parental history of

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5625) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. Periodicals postage paid at Butler, NJ, and at additional mailing offices. Postmaster: Send address changes to Psychiatry Alerts NOS, 45 Carey Ave. Ste 111, Butler, NJ 07405. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Back issues and single copies are available for \$10.00 each, prepaid. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

bipolar disorder (adjusted hazard ratio [HR],* 2.6). Other significant predictors with similar HRs included presence of psychotic depression at the index episode (HR, 1.73), presence of prior or concurrent nonaffective psychosis (HR, 1.73), and inpatient treatment of the index episode (HR, 1.76). Additional predictors with smaller but still statistically significant hazard ratios included female gender; emergency room treatment of the index episode; recurrent depression; at least moderate severity of the index episode; prior or current alcohol abuse; and parental history of unipolar depression. Despite other evidence suggesting risk is greater in young patients, age at diagnosis was not associated with conversion in this sample, possibly because registry-based studies may underestimate the conversion rate in pediatric populations.

Discussion: Based on the findings in this large, nationally representative sample, presence of severe, recurrent, or psychotic depression, comorbid alcohol abuse, and need for inpatient treatment appear to be clinically relevant predictors of conversion to bipolar depression in patients initially treated for unipolar depression. Early detection of at-risk patients could reduce the duration of untreated bipolar illness.

Musliner K, Ostergaard S: Patterns and predictors of conversion to bipolar disorder in 91587 individuals diagnosed with unipolar depression. *Acta Psychiatrica Scandinavica* 2018;137 (May):422–432. From Aarhus University; and the Lundbeck Foundation, Aarhus, Denmark. **Funded by the Lundbeck Foundation; and Aarhus University. The authors declared no competing interests.**

*See Reference Guide.

Evaluating Mental Health Apps

At least 10,000 smartphone apps now exist that target mental health, but there are no available tools that provide a reliable method of evaluating their safety or usefulness.¹ The American Psychiatric Association (APA) has created a rubric to guide clinicians in the evaluation of these apps. The rubric does not directly rate or score an app, and it does not rely on any existing user ratings. Rather, it suggests that clinicians and/or patients consider a simple 5-step evaluation process, progressing to the next stage only if the app satisfies the clinical need at the current stage. There are no specific criteria to judge whether an app is satisfactory at each hierarchical step. Instead, the APA framework includes a series of questions intended to guide a personalized determination of the appropriateness of an app for a given patient. The specific questions are available on the APA website at <https://psychiatry.org/psychiatrists/practice/mental-health-apps/app-evaluation-model>.

Step 1: Prior to evaluating an app, the clinician should gather as much useful background information as possible. Pertinent information at this stage could include the developer, cost to the patient, number of updates, and available platforms.

Step 2: Privacy and digital safety/risk should be evaluated next. At this stage, the privacy policy for the app should be carefully assessed to determine such things as: what data are collected; is data personally identifiable; can a user opt-out of data collection; what data are shared and with whom; where is the data stored; and what security measures are in place.

Step 3: If the digital safety of the app is acceptable, evidence for the effectiveness of the app should be evaluated. While some apps have documented clinical-trial efficacy, many do not. If no such evidence is found, the clinician should consider downloading and testing the app personally. User feedback may be helpful at this stage.

Step 4: If in the previous steps it was determined that the app offers minimal risk in terms of digital safety and privacy and appears to offer some benefit, ease of use can be assessed. Specific questions here could include: is the app customizable, easy to use, and culturally sensitive; and is it accessible to those with a disability.

Step 5: The final step in the hierarchy is evaluation of interoperability, specifically whether the patient and clinician can share and discuss data or feedback from the app so as not to fragment care. While this may not be relevant to all apps, it may be especially important for those that monitor mood or address medication management.

In an effort to better understand how clinicians use the model and to gather data to be used for further improvement, the APA is encouraging users to share their app evaluations on the APA Web site.²

¹Torous J, Chan R, Gipson S, Kim J, et al: A hierarchical framework for evaluation and informed decision making regarding smartphone apps for clinical care. *American Journal of Psychiatry* 2018; doi 10.1176/appi/ps.201700423. From Harvard Medical School, Boston, Mass; and other institutions. **The authors declared no competing interests.**

²American Psychiatric Association. App evaluation model Web site. <https://psychiatry.org/psychiatrists/practice/mental-health-apps/app-evaluation-model>. Accessed April 18, 2018.

Brain Morphology and Depression Relapse

A longitudinal neuroimaging study identified a distinct pattern of changes associated with relapse in patients with depression, including structures involved in regulation of emotion.¹

Methods: Study participants were 60 patients with major depressive disorder and 54 age- and gender-matched healthy controls. When enrolled, all patients were experiencing a moderate or severe depressive episode requiring inpatient treatment. Patients were divided into 2 groups based on the clinical course over the subsequent 2 years: 37 patients who experienced ≥ 1 relapse episode and 23 patients who were relapse-free. Full remission, defined as absence of symptoms for ≥ 2 months, was required before diagnosing a relapse. All patients and controls underwent brain MRI scans at study entry and 2 years later. The analysis included both gray matter volume and region-of-interest cortical thickness of the insula, medial orbitofrontal cortex (OFC), rostral anterior cingulate cortex (ACC), and rostral middle frontal gyrus. Additional analyses investigated the potential influences of medication and depression severity at follow-up.

Results: Patients and controls were in their mid-30s on average. Medication exposure, both at baseline and during follow-up, did not differ between patients who did or did not relapse. However, patients who experienced a relapse had significantly higher baseline gray matter volumes than patients without relapse (in the dorsolateral prefrontal cortex [DLPFC] only) and controls (in both the DLPFC and insula). Longitudinal whole-brain analysis identified a significant increase in gray matter volume in healthy controls ($p < 0.001$), a decrease in patients who relapsed ($p = 0.04$), and no significant change in relapse-free patients. In the rostral middle frontal gyrus, an area chosen to represent the DLPFC, patients with relapse had a significant decrease in gray matter volume ($p < 0.001$), but those without relapse and healthy controls showed no change. Neither medication status nor depression severity was associated with gray matter volumes or changes.

Longitudinal region-of-interest analysis showed significant increases in cortical thickness in the left medial OFC and left rostral ACC in patients without relapse ($p = 0.003$ and $p = 0.005$, respectively). Healthy controls also showed increases in both of these areas, while relapsed patients did not. Patients with relapse, but no other group, had a decrease of cortical thickness in the right rostral middle frontal gyrus.

Discussion: The changes observed in these patients are consistent with neurobiological models of major depressive disorder that assume a dysfunction of the frontolimbic brain circuitry. They also extend previous cross-sectional data to a non-elderly population of patients with depression and appear to be the first to account for effects of medication. While there were unexpected findings that remain unexplained—the larger DLPFC gray matter volume at baseline in patients who relapsed and the increases in gray matter volume and

cortical thickness in healthy controls—the study results suggest that neuroimaging techniques may have real-world clinical utility in identifying patients likely to relapse and finding targets for interventions, including neuromodulation, to interrupt the course of recurrent depression.²

¹Zaremba D, Dohm K, Redlich R, Grotegerd D, et al: Association of brain cortical changes with relapse in patients with major depressive disorder. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.0123. From the University of Munster, Germany; and the University of Adelaide, Australia. **Funded by the German Research Foundation; and other sources. Two of 17 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

²Phillips M: A promising future role for neuroimaging in tracking and predicting relapse in major depressive disorder [editorial]. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.0405. From the University of Pittsburgh, PA. **The author declared no competing interests.**

Creatine Kinase and Aggression

According to the results of a retrospective study, aggression is associated with elevated creatine kinase (CK) levels in patients hospitalized with schizophrenia. Evaluation of CK levels could help identify patients with the potential for aggressive behavior.

Background: CK is an enzyme that is widely used as a biological marker for heart trauma or skeletal muscle damage. It may be increased after physical trauma, intramuscular injections, seizure, neuroleptic malignant syndrome, restraint, and intense exercise. Elevated levels in patients with psychotic mania or schizophrenia could also be related to psychomotor agitation or seclusion.

Methods: Study subjects were nearly 2800 patients consecutively admitted to 5 psychiatric inpatient units of a Chinese university hospital between 2009 and 2013. All patients had a diagnosis of schizophrenia, according to DSM-IV criteria, and had CK measured as part of routine admission blood tests. Before patients received any medication, clinicians documented their aggressive behaviors, including verbal and physical aggression against self or others. Patients were not included in the analysis if they had diseases, injuries, or other events that could increase CK levels.

Results: At admission, 28% of patients had serum CK levels above the normal limits for the assay used (i.e., >226 U/L), and 5.5% of patients were classified as aggressive. Patients aged <30 years and men were overrepresented among both persons with elevated CK and those with aggressive behavior.

Aggression was more common among patients with elevated CK levels, 18% versus 2.6% in patients with CK levels in the normal range (odds ratio,* 8.1). Among patients with aggression, 61% were found to have elevated CK, compared with 16% of non-aggressive patients. A multivariate analysis that excluded CK level found aggressive behavior was also associated with male gender, alcohol abuse, drug abuse, and a history of psychosis. In most patients with elevated CK levels, prevalence of aggression decreased after hospital admission. However, in those with the highest CK levels (i.e., >5 times the upper limit of normal), the prevalence increased.

Discussion: Although the exact relationship between aggression and CK elevation remains unclear, measurement of CK along with evaluation of the other identified risk factors could help predict which patients with schizophrenia will display aggression.

Meng X-D, Cao X, Li T, Li J-P: Creatine kinase (CK) and its association with aggressive behavior in patients with schizophrenia. *Schizophrenia Research* 2018; doi 10.1016/j.schres.2018.02.025. From Sichuan University and Chengdu Medical College, Chengdu City, China. **Funded by the Natural Science Foundation of China. The authors declared no competing interests.**

*See Reference Guide.

Augmented tDCS for Resistant Depression

In a pilot study, transcranial direct current stimulation (tDCS) augmented with a simultaneous cognitive-emotional task had promising results in patients with medication-resistant depression.

Methods: Study subjects were 20 adults with medication-resistant major depressive disorder indicated by a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥ 20 despite adequate antidepressant pharmacotherapy. All participants underwent tDCS with simultaneous Cognitive Emotional Training (CET) 3 times per week for a total of 18 sessions. CET consisted of the Emotional Faces Memory Task, in which patients remembered the emotional expressions of a series of faces on a computer screen. Outcomes were assessed at baseline, mid-treatment, and at treatment end. The primary efficacy measure was change from baseline in MADRS score.

Results: Study participants' depression had not responded to a mean of 1.3 antidepressant drugs in the present episode and 4.7 over the lifetime course of their illness. Of the 20 patients enrolled, 3 did not complete treatment for personal reasons. The mean MADRS score decreased from 30 at baseline to 23 mid-treatment, and further to 18.6 at the end of treatment ($p < 0.001$). Of the 17 patients who completed treatment, 7 (41%) had a $\geq 50\%$ reduction in MADRS score, meeting criteria for treatment response. Patients also reported improvement in psychological symptoms, rumination, and quality of life. For about half of the patients, the duration of brain stimulation was increased from 30 to 40 minutes mid-study to accommodate completion of the CET; results did not differ between patients receiving the 2 tDCS durations. Patients were administered a battery of cognitive tests, but only 1, the Digit Span Total test, showed improvement with treatment. Changes in depression and in measures of cognition were not correlated.

Discussion: Prior studies have found little or no effect of tDCS in patients with medication-resistant depression. Because tDCS is a sub-threshold stimulus, it may be important to add a simultaneous task because ongoing neural activity is necessary to induce lasting neuroplastic changes. CET is hypothesized to activate the dorsolateral prefrontal cortex and the amygdala, regions involved in working memory and emotional recognition. Contrary to the investigators' expectations, CET during tDCS did not enhance cognitive performance.

Martin D, Teng J, Lo T, Alonzo A, et al: Clinical pilot study of transcranial direct current stimulation combined with Cognitive Emotional Training for medication resistant depression. *Journal of Affective Disorders* 2018;232 (May):89–95. From the University of New South Wales, Sydney, Australia; and other institutions. **Funded by the National Alliance for the Research of Schizophrenia and Depression. The authors did not include disclosure of potential conflicts of interest.**

Gene Network Mapping in Schizophrenia

Genome-wide association studies (GWAS) have identified as many as 108 independent loci, containing >300 genes, that are involved in schizophrenia. Antipsychotic drugs bind to numerous proteins, only 2 of which, dopamine and serotonin receptors, have known biological links to schizophrenia. It is highly likely that other, as-yet unidentified pathways are involved in the disease.

Methods: Risk genes for schizophrenia, as with other complex disorders, interact with one another and form a functional network. Researchers at the University of California San Diego mapped a subset of schizophrenia risk genes from the GWAS according to their interactions in order to identify a group of interconnected genes that form the core disease module. They then examined the freely available Drug-Gene Interaction database and identified 88 of these genes that were targeted by ≥ 1 of 64 antipsychotic drugs to identify interactions among drug targets and risk genes.

Results: Antipsychotic drug targets or their nearest neighboring genes were statistically associated with schizophrenia, and these connected genes tended to be involved in developmental biology, learning or memory, and cognition. Four genes were both a risk gene and a drug target gene: glutamate metabotropic receptor 3, dopamine receptor D2, cholinergic muscarinic receptor 4, and CYP2D6. Many other risk genes overlapped or connected with genes that were antipsychotic drug targets.

The investigators also identified risk genes that were not connected to antipsychotic targets as potentially druggable targets. Multiple gene clusters with potential as targets for cognitive enhancers were found, and 11 drugs approved for other indications and 8 experimental drugs were identified that could potentially target schizophrenia genes. Interestingly, 1 group of genes—nicotinic acetylcholine receptor genes—is thought to be important in the cognitive deficits of schizophrenia and also in Alzheimer’s disease. These genes are targeted by several existing drugs, including galantamine (*Razadyne*), that are currently being investigated as cognitive enhancers in schizophrenia.

Discussion: The present results indicate an overlap exists between the pathological mechanisms of schizophrenia and the pharmacological mechanisms of antipsychotics. Information regarding this overlap could be used to advance the development of more efficient multitarget drugs directed at poorly treated aspects of schizophrenia.

Kauppi K, Rosenthal S, Lo M-T, Sanyal N, et al: Revisiting antipsychotic drug actions through gene networks associated with schizophrenia. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2017.17040410. From the University of California San Diego; and other institutions. **Funded by the NIMH. Two of 9 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Reference Guide

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.

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.

YOU ASKED . . . WE DELIVERED

You told us you wanted to complete online exam modules monthly rather than at the end of the issue cycle (every 6 months). We are happy to announce that you can now do just that! Online modules will now be released shortly after the monthly issue is published.

**For additional details, or to enroll, call us at 973-898-1200
or visit www.alertpubs.com.**

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**
Founding Editor: **Michael J. Powers**

PSYCHIATRY ALERTS NOS

DBS for Depression	26
Depression, Anxiety, and Thyroid Disease.....	29
ECT and Dementia Risk.....	27
Important Notice	30
Preventive Cognitive Therapy in Depression	28
Reference Guide	30
rTMS for Suicidal Ideation	25

Volume X / May 2018 / Number 5

www.alertpubs.com

Change Coming . . . See back page for details.

Suicidal Ideation as Specific rTMS Target

According to a post-hoc analysis of clinical-trial data, bilateral repetitive transcranial magnetic stimulation (rTMS) reduced suicidal ideation independently of its effects on depressive symptoms.¹ This observation suggests rTMS may be a useful alternative to ECT in reducing suicidal ideation.

Background: Although ECT has been shown to reduce suicidality in patients with mood disorders, many patients may prefer to receive rTMS because it is less invasive, does not require anesthesia, carries less stigma, and does not have adverse cognitive effects. However, the effects of rTMS on suicidal ideation have only been studied in 2 small trials.^{2,3} The present analysis combines data from these studies in order to clarify the antisuicide effects of rTMS.

Methods: Data were combined from 2 previously published studies that compared bilateral, unilateral, and sham rTMS in patients with treatment-resistant depression that had not responded to ≥ 2 antidepressant medications of different classes in the current episode. Suicidal ideation was measured using the suicide item on the Hamilton Rating Scale for Depression (HAM-D), which is scored from 0 (absent) to 4 (any serious suicide attempt). Both studies excluded patients with active suicidality, thus no eligible patient had a suicidal ideation score of >3 . The primary study outcome was resolution of suicidal ideation, defined as a decrease from any nonzero score to 0 at the study endpoint, which could be 3–6 weeks after baseline depending on the patient's response. Change in depressive symptoms was evaluated using the 16 non-suicide items of the HAM-D.

Results: After exclusion of patients who had a suicide score of 0 at baseline, the sample consisted of 156 patients who received treatment with bilateral (n=52), unilateral (n=56), or sham (n=48) rTMS. The mean baseline suicide score was nearly 2 in all groups. Suicidal ideation resolved in 40% of patients who received bilateral rTMS, 27% of patients who received unilateral treatment, and 19% of those who received sham treatment. Patients who received bilateral treatment had a significantly higher likelihood of resolution than the sham

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5625) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. Periodicals postage paid at Butler, NJ, and at additional mailing offices. Postmaster: Send address changes to Psychiatry Alerts NOS, 45 Carey Ave. Ste 111, Butler, NJ 07405. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Back issues and single copies are available for \$10.00 each, prepaid. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

group (odds ratio,* 3.03; p=0.02). Resolution of suicidal ideation was not significantly more likely with unilateral versus sham treatment despite an odds ratio of 1.59.

The level of correlation between changes in depressive symptoms and in suicidal ideation was modest but significant (correlation coefficient,* 0.038; p<0.001). The degree of HAM-D improvement did not differ significantly between those whose suicidal ideation did and did not remit, and improvement in depression accounted for about 15% of the change in suicidal ideation.

Of the 33 patients in the initial studies excluded from the analysis because of a suicide score of 0 at baseline, new suicidal ideation developed in 1 of 14 patients receiving bilateral rTMS, 2 of 6 in the unilateral group, and 4 of 13 in the sham group.

Discussion: The rate of remission of suicidal ideation in this pooled sample was higher than the rate of remission for depression (40% vs 26% with bilateral rTMS). These results support the emerging idea that suicide may be its own transdiagnostic entity; and bilateral rTMS may be a specific treatment for suicidality. Future studies should evaluate different neuro-anatomic targets and the potential of rTMS in suicidal ideation related to other disorders such as borderline personality disorder or PTSD.

¹Weissman C, Blumberger D, Brown P, Isserles M, et al: Bilateral repetitive transcranial magnetic stimulation decreases suicidal ideation in depression. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11692. From the University of Toronto, Canada; and other institutions. **This analysis was performed without specific funding. Six study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

²Blumberger D, et al: A randomized double-blind sham-controlled comparison of unilateral and bilateral transcranial magnetic stimulation for treatment-resistant major depression. *World Journal of Biological Psychiatry* 2012;13:423–435.

³Blumberger D, et al: Unilateral and bilateral MRI-targeted repetitive transcranial magnetic stimulation for treatment-resistant depression: a randomized controlled study. *Journal of Psychiatry & Neuroscience* 2016;41:E58–E66.

*See Reference Guide.

Deep Brain Stimulation for Depression

According to results of a systematic review and meta-analysis, evidence is insufficient at this time to support the clinical use of deep brain stimulation (DBS) for refractory depression. While the treatment shows promise, it also comes with significant risks and burdens, and less invasive brain stimulation approaches are available.

Methods: A comprehensive literature search was undertaken to identify single- or double-blind, crossover or parallel-group studies published before December 2017 in which DBS was compared with sham treatment using a validated depression scale. For crossover trials, only the first phase of treatment was included, whenever possible, to avoid carryover effects. Meta-analysis compared rates of response based on study-defined improvements on the Hamilton Rating Scale for Depression (HAM-D), Beck Depression Inventory, or Montgomery-Asberg Depression Rating Scale, generally a ≥50% reduction in score or a final HAM-D score of <8.

Results: A total of 9 studies were included in the analysis: 7 double-blind randomized controlled trials, 1 single-blind sham stimulation trial before and after 24 weeks of active stimulation, and 1 single-blind study of sham treatment for 4 weeks before crossing over to active DBS. Intervention sites were the subcallosal cingulate gyrus in 5 studies, the medial forebrain bundle in 2, and the anterior limb of the internal capsule or ventral capsule/striatum in 2. Treatment duration ranged from 1 day to 26 weeks. The studies enrolled a total of 200 patients, 23 of whom dropped out, most often for reasons relating to their underlying illness, not the device.

The pooled odds ratio* for response, measured at 16 weeks, was 5.5 (p<0.00001). However, the odds ratio for response was reduced to 2.5 and was no longer statistically significant after exclusion of the 5 crossover studies. In the 8 studies that reported mean reductions in depression score compared with sham stimulation, the mean reduction was -0.42 standard deviations

($p=0.006$). Differences in secondary outcomes, including global functioning and quality of life, did not differ significantly between the groups.

A total of 131 serious adverse events occurred in 84 patients. These included worsening depression or anxiety in 29 patients, suicidal ideation in 12, and infection in 7. It was not always clear whether these effects were related to the surgery or to brain stimulation. Many other adverse effects were transient and related to the stimulation, including hypomanic symptoms, sleep disturbance, disinhibition, agitation/restlessness, nausea/vomiting, and headache.

Discussion: Based on the limited number of studies available, each with important methodological limitations, DBS may be an effective treatment for depression. However, serious adverse effects appear to be common. The authors recommend using other less-invasive brain stimulation procedures such as repetitive transcranial magnetic stimulation, magnetic seizure therapy, or vagus nerve stimulation, all of which are associated with fewer adverse effects.

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

Kisely S, Li A, Warren N, Siskind D: A systematic review and meta-analysis of deep brain stimulation for depression. *Depression and Anxiety* 2018;35 (May):468–480. From the University of Queensland Southern Clinical School, Australia; and other institutions. **Funded by the University of Queensland; and the National Health and Medical Research Council. The authors declared no competing interests.**

*See Reference Guide.

Dementia Risk After ECT

Several small studies and case reports have raised concern about the potential for an increased risk of dementia following ECT. However, results of a large registry-based cohort study do not support the association.

Methods: The study cohort, drawn from the Danish National Patient Registry, consisted of all individuals aged ≥ 10 years who received an affective disorder diagnosis between 2005 and 2015. A subsample of the population consisted of men evaluated for the military draft between 1939 and 1959 who received the affective disorder diagnosis after 2004. This subcohort provided information for a separate analysis that included baseline cognitive function. The number of ECT treatments was dichotomized as ≤ 10 and > 10 , based on the median number of sessions necessary for remission. The study outcome was an incident diagnosis of dementia between 2005 and 2016. To minimize possible biases, alternative analyses were conducted using adjustment for a long list of covariates, propensity score matching,* and a 2-year lag time between the last ECT and a dementia diagnosis, to eliminate the chance of mistaking post-ECT cognitive deficits for dementia. A competing mortality risk analysis was also conducted to account for the possibility that early death might preclude a diagnosis of dementia.

Results: More than 168,000 patients with a mean age of 47 years were included in the analysis, of whom 5901 (3.5%) received ECT. The military sample consisted of nearly 13,600 men with an affective disorder, of whom 925 (6.8%) received treatment with ECT. A total of 5204 patients in the full cohort (3.1%) had onset of dementia during the study years. Rates of dementia diagnosis ranged from 0.1% of patients aged < 50 years to 12.5% of those aged ≥ 70 years.

The incidence of dementia was higher in patients who had undergone ECT (70 vs 59 cases per 10,000 person-years), but this difference was eliminated after adjustment for covariates and in the propensity score-matched model. In the propensity score-matched analysis, in patients aged ≥ 70 years, undergoing > 10 ECT treatments was associated with significantly reduced dementia incidence (hazard ratio,* 0.59; $p=0.003$). In the sample of military draftees, ECT was associated with dementia risk only in those with the lowest premorbid cognitive ability, but this observation was based on a very small number of cases.

Discussion: Although the incidence of dementia in this study population with affective disorders was 2–3 times higher than the general population, undergoing ECT did not appear to confer additional risk. The data from the military subsample suggest that reduced cognitive reserve is not likely to influence dementia risk, except perhaps at the lowest level of premorbid cognitive function.

Osler M, Rosing M, Christensen G, Andersen P, et al: Electroconvulsive therapy and risk of dementia in patients with affective disorders: a cohort study. *Lancet Psychiatry* 2018;5 (April):348–356. From Bispebjerg and Frederiksberg Hospitals, Denmark; and other institutions. **Funded by the Danish Council for Independent Research; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Preventive Cognitive Therapy and Depression Relapse

In a randomized trial, adding preventive cognitive therapy (PCT) to maintenance antidepressant therapy provided better relapse prevention than either antidepressants alone or PCT with an antidepressant taper.

Background: Many patients at risk for depressive relapse are not willing to continue antidepressants for long periods of time, and there is evidence that some patients may become resistant to the preventive effects of antidepressants over time. Results of previous studies of PCT suggest it may have relapse-preventive effects that are equivalent to antidepressant maintenance, but it is unclear whether adding PCT would allow for antidepressant taper and if combining the treatments would have greater efficacy.

Methods: Study participants were adults with a history of multiple major depressive episodes whose symptoms were currently in remission (i.e., Hamilton Rating Scale for Depression [HAM-D] score ≤ 10) for between 8 weeks and 2 years. To be eligible for the study, patients had to have achieved remission using antidepressant medications and to have been receiving pharmacotherapy for ≥ 6 months. PCT is a manualized program consisting of 8 weekly sessions, aimed at identifying dysfunctional attitudes, enhancing memories of positive experiences, and formulating preventive strategies. PCT was initially offered in a group format, but individual therapy was added because many patients could not attend group sessions. Participants were randomly assigned to receive PCT with an antidepressant taper, PCT with ongoing maintenance antidepressants, or antidepressant maintenance alone. Outcomes were assessed after 3, 9, 15, and 24 months by blinded raters. The primary study outcome was the time to recurrence of depression over 24 months.

Results: The study enrolled 289 participants over a 6-year period. Before randomization, 69% had ≥ 4 months of sustained remission. A total of 209 patients with available follow-up data were included in the analysis. Of patients still in the study after 6 months, about 60% were compliant with their continued medication or with the taper. Most who received PCT completed 5 of the 8 sessions: 68 (88%) in the combined-treatment group and 57 (90%) who tapered antidepressants.

PCT with taper and antidepressant maintenance had similar results, while the treatment combination was superior to both. (See table.) The estimated cumulative incidence of relapse over 2 years was similar in the group receiving PCT with antidepressant tapering and the group receiving antidepressant

Relapse Risk Over 2 years			
Treatment	Comparison	Hazard Ratio*	Significance
Antidepressants alone	PCT with taper	0.86	p=ns
Combined treatment	Antidepressants alone	0.59	p=0.026
Combined treatment	PCT with taper	0.54	p=0.011

maintenance alone (63% and 60%, respectively), although relapses tended to occur more often in the first 140 days in patients whose antidepressant was tapered. The estimated recurrence rate in patients receiving both PCT and continued antidepressants was 43%. Combining PCT with maintenance antidepressants also had positive effects on secondary outcomes, including a reduced number and shorter duration of recurrences.

Discussion: Results of this study suggest PCT should be offered to patients who have recovered after recurrent depression and who wish to stop their antidepressants, as well as to those who intend to continue their medication.

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

Bockting C, Klein N, Elgersma H, van Rijsbergen G, et al: Effectiveness of preventive cognitive therapy while tapering antidepressants versus maintenance antidepressant treatment versus their combination in prevention of depressive relapse or recurrence (DRD study): a three-group, multicentre, randomised controlled trial. *Lancet Psychiatry* 2018;5 (May):401–410. From the University of Amsterdam, the Netherlands; and other institutions. **Funded by the Netherlands Organisation for Health Research and Development. Two of 13 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Depression, Anxiety, and Thyroid Disease

A systematic review and meta-analysis found significant associations between presence of autoimmune thyroid disease and depression and anxiety. Although the study could not confirm the association as causal, there is evidence to support an autoimmune basis for some psychiatric disorders.

Methods: A comprehensive literature search identified studies published between 1992 and 2017 evaluating depression and/or anxiety using standardized measures in patients with and without autoimmune or Hashimoto's thyroiditis, overt hypothyroidism, or latent or subclinical hypothyroidism.

Results: Meta-analysis of the 19 identified studies (>36,000 patients) found thyroid disease significantly increased risk for both depression and anxiety disorders. Risk for depression was increased >3-fold (odds ratio,* 3.56; $p<0.001$). Most studies that examined anxiety used a self-report instrument such as the State-Trait Anxiety Inventory, the Beck Anxiety Inventory, or the Hospital Anxiety and Depression Scale. As a result, it was not possible to analyze the association of autoimmune thyroiditis with specific anxiety disorders. However, risk for anxiety disorders overall was increased >2-fold (odds ratio, 2.32; $p<0.001$) in patients with autoimmune thyroiditis.

Discussion: These results suggest that thyroid disease and depression/anxiety are likely to co-occur. Laboratory testing for thyroid disease, including levels of thyroid stimulating hormone, free T3 and T4, as well as thyroid peroxidase antibodies (a more sensitive indicator of autoimmune disease), may be useful in patients presenting with depression or anxiety, as those with autoimmune thyroiditis require an adapted treatment approach. Levothyroxine treatment and selenium supplementation can improve mood symptoms. Thyroid function affects the serotonin system, making SSRIs an appropriate option when antidepressants are required. TCAs may not be suitable for patients with autoimmune thyroiditis who are already likely to gain weight.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis. However, the authors did not disclose the study's source of funding.

Siegmann E, Muller H, Luecke C, Philipsen A, et al: Association of depression and anxiety disorders with autoimmune thyroiditis: a systematic review and meta-analysis. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.0190. From Friedrich-Alexander University Erlangen-Nuremberg, Germany; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

*See Reference Guide.

Reference Guide

Correlation Coefficient (r): A measure of the closeness of the relationship between 2 variables. The value of r can range from -1 to 1. An r value near 1 indicates a strong positive relationship. An r-value close to zero indicates no relationship, and a negative r-value indicates a negative relationship.

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.

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

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

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

**"Change is the law of life and those who look only to the past or present
are certain to miss the future."—John F. Kennedy**

Starting with the August issue, the delivery of *Psychiatry Alerts NOS* will be 100% electronic; we are leaving the printing to you. The content of the newsletter will be unchanged; only the method of delivery will change. Why?

- The majority of our readers prefer to read their issues of *Psychiatry Alerts NOS* online—either through the email they receive before the paper version is even mailed or directly from our website. The electronic version is a PDF document and reads very clearly on any computer or device. And there's always the option to print it yourself.
- The U.S. Postal Service has become increasingly slow and unreliable. Our customer service representatives spend a disproportionate amount of time replacing issues that were lost in the mail.
- The price of printing, paper, and mailing have become prohibitively expensive over the years—too much for a small publisher to absorb without increasing prices significantly.

Please note that our **CME exams will be printed and mailed to you as usual.** There will be no change to the CME program.

The easiest way to continue receiving *Psychiatry Alerts NOS* is through email. If you have not yet done so, please register your email address with us by logging in to your account at www.alertpubs.com with your customer number (see envelope) and using the "Change Address" feature at the top of the page. Check that all of your information is correct, and add your email address in the last box. If you don't have an online account, you can quickly and easily create one on the website. And don't worry, we will never share your email address without your permission.

You can also log on to www.alertpubs.com at your convenience each month to see the current issue, as well as back issues.

Please let us know if you need help accessing your monthly issues. Email Donna at customerservice@alertpubs.com or call her between the hours of 9 AM and 3 PM EST weekdays.

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**

PSYCHIATRY ALERTS NOS

Circadian Activity and Mood.....	35
Important Notice	36
Ketamine Anesthesia for ECT.....	31
mHealth for Serious Mental Illness	33
Nightmare Disorder Treatments.....	34
Reference Guide	36
TMS plus Behavioral Activation Therapy.....	32

Volume X / June 2018 / Number 6

www.alertpubs.com

Change Coming . . . See back page for details.

Ketamine Anesthesia and ECT Outcomes

Compared with propofol-based anesthesia, ketamine-based anesthesia reduced the number of ECT sessions needed for response in patients with treatment-resistant depression in a randomized trial.

Methods: Study participants had a diagnosis of treatment-resistant depression, a baseline Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥ 20 , and had been referred to a university hospital for ECT treatment. Patients were randomly assigned to anesthesia with either ketamine or propofol, both used in conjunction with remifentanyl and succinylcholine. The study pharmacist prepared the anesthesia beforehand, and the anesthesiologist was permitted to vary the doses of the other agents, without being aware of the randomized treatment. All patients were enrolled for 8 ECT sessions, 2 or 3 times per week, with unilateral or bilateral electrode placement and ECT parameters determined by the attending psychiatrist. The MADRS was administered 1 day after each ECT session and 30 days after the final session. The primary study outcome was the number of ECT sessions needed to achieve response, defined as a $\geq 50\%$ reduction in MADRS score. Remission was defined as a MADRS score of ≤ 10 . The study was terminated after an interim analysis due to early efficacy results.

Results: Of the 27 study participants, all 14 patients in the ketamine group and 10 of 13 in the propofol group met MADRS criteria for response. The median number of treatments before response was 2 for ketamine and 4 for propofol ($p=0.01$). All patients in the ketamine arm achieved remission, which occurred after a median of 3 treatments. In the propofol group, 7 patients achieved remission after a median of 7 sessions. A single patient in each group experienced a relapse of depression during the 30-day follow-up. There were no significant differences between the 2 anesthetics in adverse effects, which included hemodynamic changes, nausea/vomiting, and headache. Ketamine resulted in no dissociation and only rare memory impairment, but the dose was relatively low. Average time from anesthesia induction to discharge readiness was the same in both groups, about 1 hour.

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5625) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. Periodicals postage paid at Butler, NJ, and at additional mailing offices. Postmaster: Send address changes to Psychiatry Alerts NOS, 45 Carey Ave. Ste 111, Butler, NJ 07405. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Back issues and single copies are available for \$10.00 each, prepaid. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

Discussion: Earlier studies and meta-analyses of ketamine-based anesthesia in ECT have had conflicting results. Inconsistencies may have resulted from differences in electrode placement, stimulus parameters, ketamine dosing, or the use of sedatives that can suppress seizures and reduce the efficacy of ECT. Although the present results are positive, they require replication. In addition, the potential adverse cardiovascular effects of hemodynamic changes associated with ketamine administration should be evaluated.

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

Gamble J, Bi H, Bowen R, Weisgerber G, et al: Ketamine-based anesthesia improves electroconvulsive therapy outcomes: a randomized-controlled study. *Canadian Journal of Anesthesia* 2018; doi 10.1007/s12630-018-1088-0. From the University of Saskatchewan, Canada. **Funded by the University of Saskatchewan; and the Royal University Hospital Foundation. The authors declared no competing interests.**

Common Drug Trade Names: ketamine—*Ketalar*; propofol—*Diprivan*; remifentanyl—*Ultiva*; succinylcholine—*Anectine*

*See Reference Guide.

TMS Augmented by Behavioral Activation Therapy

Results of a pilot study suggest that adding behavioral activation therapy (BAT), modified to be delivered during transcranial magnetic stimulation sessions, is feasible and has the potential to improve outcomes in patients with resistant depression.

Background: Both TMS and BAT have been shown to be effective in the treatment of major depression. TMS has been shown to increase reward learning and may have the ability to "prime" patients to be more sensitive to reinforcements from BAT activities. Ordinarily, BAT is delivered in 45–60 min weekly sessions by providers trained in counseling. The present study was undertaken to investigate whether BAT could be adapted to be delivered by TMS technicians during sessions.

Methods: The investigators developed a protocol in which BAT was modified to fit the structure of daily TMS sessions. Treatment was provided by nurses or Bachelor's-level technicians who had completed about 10 hours of training. Patients were introduced to BAT during the first week of TMS, and engagement in activities began in week 2. Patients' progress was assessed during the first 5–10 min of each session, before starting TMS, and the next behavioral goal was discussed after TMS. Target activities were selected using an abbreviated version of the Pleasant Events Schedule. Depression was assessed as part of routine care, using the self-report Inventory of Depressive Symptomatology (IDS-SR), the 9-item Patient Health Questionnaire (PHQ-9), and the Snaith-Hamilton Pleasure Scale (SHAPS), a 14-item self-report measure of anhedonia. Criteria for response were a $\geq 50\%$ decrease from baseline in the IDS-SR and the PHQ-9. A $\geq 50\%$ change in SHAPS score indicates a significant decrease in anhedonia.

Results: A preliminary analysis was performed on data collected over 14 weeks from 11 patients, all women. Patients had completed a mean of 33 TMS sessions. They set a mean of 18 behavioral activation goals and completed a mean of 14. A total of 6 patients (55%) met clinical criteria for response. Mean decreases on the standardized depression measures ranged from 39% for the SHAPS to 55% for the PHQ-9. Although it did not reach statistical significance, patients' percent of goal completion correlated positively with change in measures of depression severity. After treatment completion, many patients said they intended to continue applying behavioral activation in their daily lives. TMS technicians reported anecdotally that BAT did not impair the flow of TMS delivery and that it enhanced the quality and efficiency of daily clinical assessments.

Discussion: Although the study was inadequately powered to demonstrate a significant relationship between BAT participation and depression symptom measures, the overall positive

direction of the correlations suggests that further investigation is warranted. Future studies should compare the combination of BAT and TMS with standard TMS alone in a larger sample.

Russo G, Tirrell E, Busch A, Carpenter L: Behavioral activation therapy during transcranial magnetic stimulation for major depressive disorder. *Journal of Affective Disorders* 2018;236 (August 15):101–104. From Alpert Medical School of Brown University, Providence, RI; and other institutions. **This study was conducted without specific funding. The authors declared no competing interests.**

Smartphone Intervention for Serious Mental Illness

In a randomized trial in patients with serious mental illness, a smartphone-based self-management intervention and a clinic-based program had similar effects. Both treatments had high patient satisfaction, but the mobile phone-based health (mHealth) intervention higher rates of patient engagement.

Methods: FOCUS, the mHealth intervention, was compared with the Wellness Recovery Action Plan (WRAP), a clinic-based group intervention widely used for patients with schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder. The interventions were delivered over 12 weeks at a large mental health services agency in the Midwestern U.S. FOCUS consists of a smartphone app, a clinician dashboard, and an mHealth support specialist. The app has daily self-management prompts and assessments and on-demand video or audio content about auditory hallucinations, mood, sleep, social functioning, and medication. Study participants received brief weekly calls from an mHealth specialist for technical and clinical support. WRAP is an in-person group program led by trained facilitators, with similar goals and techniques to FOCUS. Patients were randomly assigned to 1 of the 2 interventions in 12-week parallel-group cycles. The primary clinical outcome, assessed by blinded raters, was change from baseline to post-treatment (3 months) and follow-up (6 months) in general psychopathology, measured using the brief Symptom Checklist-9 (SCL-9).

Results: A total of 163 patients (mean age, 49 years; 59% men) were randomized. About half of participants had schizophrenia or schizoaffective disorder, 28% had bipolar disorder, and 23% had major depression. More than two-thirds had previously used a smartphone.

After randomization, 90% of patients randomized to FOCUS started using the app, compared with the 58% of the WRAP group who attended the first clinic session ($p < 0.001$). Although daily use of FOCUS declined during the trial, patients used the app on at least half of the days in every week, averaging 5.4 days in the first week and 3.8 days in the final week. Patients were more likely to fully engage in FOCUS than WRAP for ≥ 8 weeks (56% vs 40%; $p = 0.03$). Mean posttreatment satisfaction was similar for the 2 interventions.

Results of treatment did not differ between the 2 groups for any of the primary or secondary clinical outcomes at 3 months. Mean SCL-9 scores decreased significantly from baseline to 3 months and 6 months in both the FOCUS and WRAP groups. The 2 interventions were associated with similar significant improvements on the Beck Depression Inventory and the Recovery Assessment Scale at 6 months. Neither group demonstrated significant improvement in Psychotic Symptom Rating Scales score or quality of life at 3 months, although these measures did reach significance at 6 months in the FOCUS group.

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

Ben-Zeev D, Brian R, Jonathan G, Razzano L, et al: Mobile health (mHealth) versus clinic-based group intervention for people with serious mental illness: a randomized controlled trial. *Psychiatric Services* 2018; doi 10.1176/appi.ps.201800063. From the University of Washington, Seattle; and other institutions. **Funded by the Patient-Centered Outcomes Research Institute. One of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Treating Nightmare Disorders

Nightmare disorders are common, affecting 4% of the U.S. adult population. Diagnostic criteria proposed in the third edition of the International Classification of Sleep Disorders are repeated occurrences of extended, extremely dysphoric dreams; rapid alertness on awakening; and clinically significant distress or impairment in important areas of functioning. Nightmares may occur without comorbid psychopathology or may be associated with such disorders as depression, anxiety, substance abuse, borderline personality, PTSD, and schizophrenia-spectrum disorders. PTSD-associated nightmares have been the most studied.

An updated position paper from the American Academy of Sleep Medicine acknowledges that there is limited direct evidence for most of the available treatment options. The task force based its treatment recommendations on clinical expertise and qualitative assessment of the evidence, rather than using an evidence grading system. Of the many treatments available (see table), only 1 is recommended by the position paper task force: image rehearsal therapy for PTSD-associated nightmares and nightmare disorder. A few medications are "not recommended" for nightmare disorder because of evidence that they are ineffective or harmful. Most treatment options are categorized as "may be used," based on less clear evidence or consensus. The treatments in the table are listed in alphabetical order as there is no order of preference.

The only "recommended" therapy, image rehearsal therapy, is a modified CBT technique that involves altering the content of a nightmare by creating a new set of positive images and rehearsing the rewritten dream scenario daily while awake. Multiple randomized trials have evaluated the effects of this treatment on various outcomes. In a 6-month trial in 168 women survivors of sexual assault, 3 sessions of image rehearsal therapy reduced nightmare frequency by about 65%. Other trials with smaller sample sizes have described similar results. Patient populations have included veterans with PTSD and

Treatment options for nightmares in adults with PTSD-associated nightmares		
Behavioral or Psychological		
Recommended	Image rehearsal therapy	
May be used	Cognitive behavioral therapy (CBT) CBT for insomnia Exposure, relaxation, and rescripting therapy Eye movement desensitization and reprocessing	
Pharmacologic		
May be used	Aripiprazole Clonidine Cyproheptadine Fluvoxamine Gabapentin Nabilone Olanzapine	Phenelzine Prazosin [‡] Risperidone Topiramate Trazodone Tricyclic antidepressants
Treatment options for nightmare disorder		
Behavioral or Psychological		
Recommended	Image rehearsal therapy	
May be used	CBT Exposure, relaxation, and rescripting therapy Hypnosis Lucid dreaming therapy Progressive deep muscle relaxation	Sleep dynamic therapy Self-exposure therapy Systematic desensitization Testimony method
Pharmacologic		
May be used	Nitrazepam Prazosin [‡] Triazolam	
Not recommended	Clonazepam Venlafaxine	
[‡] Downgraded from a previous "recommended" status based on a recent negative study in >300 veterans with PTSD		

patients with chronic nightmares, generalized anxiety disorder, or various comorbid psychiatric disorders. A single trial in veterans with PTSD reported no benefit.

Morgenthaler T, Auerbach S, Casey K, Kristo D, et al: Position paper for the treatment of nightmare disorder in adults: an American Academy of Sleep Medicine position paper. *Journal of Clinical Sleep Medicine* 2018;14 (June 15):1041–1055. From the Mayo Clinic, Rochester, MN; and other institutions. **Funded by the American Academy of Sleep Medicine. The study authors declared no competing interests.**

Common Drug Trade Names: aripiprazole—*Abilify*; clonazepam—*Klonopin*; clonidine—*Catapres*; cyproheptadine—*Periactin*; fluvoxamine—*Luvox*; gabapentin—*Neurontin*; nabilone—*Cesamet*; nitrazepam (not available in the U.S.)—*Mogadon*; olanzapine—*Zyprexa*; phenelzine—*Nardil*; prazosin—*Minipress*; risperidone—*Risperdal*; topiramate—*Topamax*; trazodone—*Desyrel*; triazolam—*Halcion*; venlafaxine—*Effexor*

Circadian Activity and Mood

In a large, cross-sectional, population-based study, disrupted circadian rhythmicity was associated with depression, bipolar disorder, subjective wellbeing, personality, and cognitive performance. Reduced circadian amplitude, easily measured with a wrist accelerometer, may be a core feature of depressive and bipolar disorders and may help identify patients who could benefit from specific therapies.

Background: Circadian disruption is a known feature of mood disorders, but most research to date has focused on sleep-related factors or self-reported preferences for morning or evening activity. Using data from the large U.K. Biobank general population cohort, which includes objectively measured circadian rhythmicity parameters, the present study evaluated associations between circadian rhythmicity and mental health and wellbeing phenotypes, including lifetime history of mood disorder.

Methods: Study participants were selected from >500,000 adults enrolled in the U.K. Biobank project. At the baseline assessment, in 2006–2010, participants provided data on demographics, smoking, and other covariates. Accelerometer data were collected during 2013–2015 from >100,000 participants who wore the devices for 7 days during normal life. For the present analysis, the cohort was divided into quintiles based on relative amplitude of activity—i.e., the difference between the most active continuous 10-hour period and the least active 5-hour period in an average 24-hour day. Relative amplitude ranges from 0 to 1, with lower values attributable to increased nighttime activity, reduced daytime activity, or both. Cohort members with sleep disorders or insomnia were excluded from the sample. A total of 91,105 participants also completed an online version of the Mental Health Questionnaire (MHQ) in 2016–2017 and were included in the present analysis. The MHQ assessment, completed an average of 1.85 years after accelerometer recordings, obtained information on childhood trauma, lifetime mood disorders, subjective wellbeing, loneliness, and neuroticism. Brief online cognitive tests were also completed at this time.

Results: The mean relative amplitude of circadian activity in the entire population was 0.87 (range, 0.121–0.997). Lower amplitude was associated with higher prevalences of major depressive disorder and bipolar disorder and with higher ratings for neuroticism and loneliness. (See table). Higher amplitudes were

Reduction in relative amplitude and mental health and wellbeing outcomes [†]		
Outcome	Odds Ratio*	Significance
Lifetime major depressive disorder	1.06	p<0.0001
Lifetime bipolar disorder	1.11	p=0.007
Mood instability	1.02	p=0.004
Neuroticism	1.01	p<0.0001
Happiness	0.91	p<0.0001
Health satisfaction	0.90	p<0.0001
Loneliness	1.09	p<0.0001
Reaction time	1.75	p<0.0001

[†]Fully adjusted model (i.e., age, gender, ethnicity, socioeconomic deprivation, smoking status, alcohol intake, body mass index, and childhood trauma). Odds ratios represent the increase in incidence associated with a 1-quintile reduction in relative amplitude of activity.

associated with better subjective ratings of happiness and health satisfaction. Participants with lower-amplitude rhythmicity performed more poorly on the reaction time test, a measure of general neurocognitive function.

Discussion: The present study, with its very large sample size and control for various confounders, confirms the association of circadian disruption with mood disorders, risk factors for mood disorders, and neurocognitive impairment. However, because the data are cross-sectional, the results cannot address causality of the association.

Lyall L, Wyse C, Graham N, Ferguson A, et al: Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: a cross-sectional study of 91 105 participants from the UK Biobank. *Lancet Psychiatry* 2018;5 (June):507–514. From the University of Glasgow, U.K.; and other institutions. **Funded by the Wellcome Trust; and other sources. One study author disclosed a potentially relevant relationships; the remaining 14 authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

"Change is the law of life and those who look only to the past or present are certain to miss the future."—John F. Kennedy

Starting with the August issue, the delivery of *Psychiatry Alerts NOS* will be 100% electronic; we are leaving the printing to you. Please note that our CME exams will be printed and mailed to you as usual. There will be no change to the CME program.

The easiest way to continue receiving *Psychiatry Alerts NOS* is through email. If you have not yet done so, please register your email address with us by logging in to your account at www.alertpubs.com with your customer number (see envelope) and using the "Change Address" feature at the top of the page. If you don't have an online account, you can quickly and easily create one on the website. **And don't worry, we will never share your email address without your permission.**

You can also log on to www.alertpubs.com at your convenience each month to see the current issue, as well as back issues. If you need help accessing your monthly issues, email Donna at customerservice@alertpubs.com or call her at 973-898-1200 between the hours of 9 AM and 3 PM EST weekdays.

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**
Founding Editor: **Michael J. Powers**

Statement of Editorial Policy: All of the information and opinions presented in each *Psychiatry Alerts NOS* article are strictly those contained in the cited article unless otherwise noted. Reader comments are welcome by mail, by telephone, or by email.

PSYCHIATRY ALERTS NOS

Cognitive/Exposure Therapy for Hoarding	40
Important Reminder	42
Mantram Repetition for PTSD	38
Mitochondrial Agents for Bipolar Disorder.....	40
PRIME App for Schizophrenia	37
Psychoeducation in Bipolar Disorder	39
Reference Guide	42
rTMS for Anxiety/Insomnia	41

Volume X / July 2018 / Number 7

www.alertpubs.com

Change Coming . . . See back page for details.

Mobile Motivational App for Schizophrenia

Motivational deficits are crucial in determining outcomes in schizophrenia, are best addressed early in the course of the disease, and do not generally respond to traditional treatment approaches. According to the results of a randomized trial, the personalized real-time intervention for motivational enhancement (PRIME) smartphone app, designed to improve motivation, was effective, feasible, and acceptable in adolescents and young adults with schizophrenia.

Methods: Participants were recruited using online classifieds, message boards, and flyers in clinics. The trial enrolled patients from 13 states, Canada, and Australia. Patients were aged 16–36 years, met DSM-IV-TR criteria for any schizophrenia spectrum disorder, and were within 5 years of first diagnosis. They were guided through informed consent over the telephone; tasks and questionnaires were administered using an online platform; and interview-based assessments were done using internet telephony. The PRIME intervention consisted of a supportive online community; a list of long-term goals and suggested activities, graded in difficulty, to complete for each goal; and on-demand access to motivation coaches. The comparison group received 12 weeks of wait-list treatment as usual, followed by the option to receive PRIME. The primary study outcome, motivation, was assessed after 12 weeks using the Trust Task, in which the patient had a series of interactions with simulated social partners. Feasibility was assessed with usage statistics.

Results: A total of 43 patients were randomly assigned to the PRIME or control groups. Of these, 19 of 22 patients in the PRIME group completed treatment, and 19 of the 21 wait-listed participants remained in follow-up and chose to use PRIME after 12 weeks. Most patients (86%) were taking an antipsychotic medication at study entry, but these were required to have been unchanged for ≥ 1 month before entry and throughout the study.

Compared with the waitlist group, patients who received PRIME had larger increases in several components of the Trust Task: anticipated pleasure during the task ($p=0.02$; effect size,* 0.64), effort expended to increase the likelihood of future interactions with positive outcomes ($p=0.03$;

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5625) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. Periodicals postage paid at Butler, NJ, and at additional mailing offices. Postmaster: Send address changes to Psychiatry Alerts NOS, 45 Carey Ave. Ste 111, Butler, NJ 07405. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Back issues and single copies are available for \$10.00 each, prepaid. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

effect size, 0.58), and a near-significant improvement in learning from positive outcomes ($p=0.07$). Participants in the PRIME intervention also had significant improvement in several secondary outcomes, relative to controls: depressive symptoms, defeatist beliefs, and self-efficacy, with effect sizes ranging from 0.59 to 0.64. Improvements generally persisted after 3 months of follow-up.

Patients rated their overall satisfaction with PRIME at a mean of 8.2 on a 10-point scale. Participants logged in an average of 4 days per week and frequently interacted with each other and with the coach. Many patients noted that this was their first contact with other young people with a schizophrenia spectrum disorder. On-demand coaching was the best-liked feature of the program, and participants initiated contacts with coaches 10 times more often than contact with peers.

Discussion: In addition to supporting the feasibility and effectiveness of the PRIME intervention as an adjunctive treatment, the study also demonstrated that it is possible to launch and conduct a clinical trial entirely remotely, with no in-person contact with study subjects.

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

Schlosser D, Campellone T, Truong B, Etter K, et al: Efficacy of PRIME, a mobile app intervention designed to improve motivation in young people with schizophrenia. *Schizophrenia Bulletin* 2018; doi 10.1093/schbul/sby078. From the University of California, San Francisco; and other institutions including IDEO, Palo Alto, CA. **Funded by the NIH. The authors declared no competing interests.**

*See Reference Guide.

Mantram Repetition for PTSD

In a randomized controlled trial, mantram repetition therapy was an effective treatment for posttraumatic stress disorder in military veterans. The therapy may appeal to veterans who prefer a treatment that is non-trauma focused and includes some elements of spirituality.

Methods: The experimental program was based on silently repeating a mantram, a spiritually related word or phrase selected by each patient from a recommended list. This practice is believed to help patients focus attention, relax, and be aware of the present moment. Two other skills were also taught: "slowing down" thoughts and "one-pointed attention." Patients were taught to use these techniques to interrupt stressful feelings and to manage behavioral symptoms. The comparison treatment, present-centered therapy, is a supportive treatment with demonstrated efficacy in PTSD that has been used as an active comparator in other trials. Both treatments were delivered one-on-one in 8 weekly 1-hour sessions using standardized manuals. Study participants were treatment-seeking veterans with ≥ 1 traumatic experience and meeting DSM-IV-TR criteria for PTSD. Background medications were continued, and patients were asked to avoid other psychotherapy or complementary therapy. A total of 173 patients were randomly assigned to treatment. About 85% were men, and 65% were receiving medication for PTSD. The primary study outcomes were change from baseline on the Clinician-Administered PTSD Scale (CAPS) and self-reported symptoms on the PTSD Checklist–Military (PCL-M).

Results: Patients in the mantram group demonstrated significantly greater improvement in CAPS score at the end of treatment ($p=0.006$; effect size,* 0.49) and at 2-month follow-up ($p=0.04$; effect size, 0.46). Improvements in self-reported symptoms were also significantly greater with mantram repetition at the end of treatment ($p=0.04$; effect size, 0.43), but not at follow-up. At 2 months, 59% of the mantram group who remained in follow-up no longer met criteria for PTSD, compared with 40% of the present-centered therapy group ($p<0.04$). The proportion of patients who had clinically significant improvement (i.e., a ≥ 10 -point reduction in CAPS score) did not differ significantly between groups: 75% for mantram

repetition and 61% of the present-centered therapy group. Patients who used mantram repetition had significantly greater improvement in insomnia ($p < 0.05$), but other secondary outcomes, including depression, anger, spiritual well-being, mindfulness, and quality of life, improved to a similar extent in both groups.

Discussion: While it is premature, based on the present results, to suggest that mantram repetition therapy is similarly effective to cognitive processing therapy or prolonged exposure (the 2 evidence-based psychotherapies currently used by the VA for PTSD treatment), the authors note that the effect size in this study for CAPS score reduction is generally similar to or greater than the effect sizes observed for these treatments.

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

Bormann J, Thorp S, Smith E, Glickman M, et al: Individual treatment of posttraumatic stress disorder using mantram repetition: a randomized clinical trial. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2018.17060611. From the VA San Diego Healthcare System, CA; and other institutions. Funded by the VA. The authors declared no competing interests.

*See Reference Guide.

Psychoeducation in Bipolar Disorder

According to a systematic review, there is considerable randomized clinical trial support for the positive effects of group and family psychoeducation in managing bipolar disorder. There are fewer trials of individual and internet-based psychoeducation, and those trials show mixed or no effects.

Background: Psychoeducation is not limited to providing information but refers to therapist-led, personalized behavioral training that involves the patient and family members in the same session or separate sessions, or within groups. This systematic review was conducted to compare the evidence for these 3 formats and internet-based psychoeducation.

Methods: A comprehensive literature search was undertaken to identify all English-language, randomized controlled trials of each type of psychoeducation. Studies were required to use standardized assessments to evaluate clinical outcomes (e.g., symptom severity), treatment outcomes (e.g., adherence), or functioning (e.g., quality of life). In nearly all cases, treatment-as-usual was the study comparator.

Results: The review identified 8 trials of individual psychoeducation in >600 patients, 18 trials of group psychoeducation in >2300 patients, 10 trials of family psychoeducation in >750 families, and 4 trials of internet psychoeducation in >770 patients. The average follow-up duration was 15 months. Individual psychoeducation was associated with shorter depressive episodes in 1 study, but effects on symptom severity, relapse, and quality of life were inconsistent across the remaining studies. In the internet psychoeducation studies, patients and controls did not differ in recurrences, illness perception, or quality of life.

The majority of studies of group and family psychoeducation reported positive findings, which extended to a wide range of outcomes. Studies of group psychoeducation showed reductions in symptom severity, affective episodes recurrence, the number and duration of hospitalizations, and bipolar disorder-associated stigma. Treatment adherence was positively impacted by group psychoeducation, as was overall functioning. Family psychoeducation was also associated with improvements in symptom severity, reductions in relapse and rehospitalization rates, and longer relapse-free intervals, as well as lowered levels of illness burden in the patients. In addition, family members reported increases in caregiver knowledge, skills, support, and wellbeing; a more positive family attitude; and reduced levels of family burden.

Discussion: Many of the positive effects of the group and family formats are likely to be inter-related. For example, with group psychoeducation, better treatment adherence probably results in more optimal therapeutic medication levels and improved clinical outcomes. Decreased stigma through group psychoeducation may also contribute to improved clinical outcomes. Discussions in group psychoeducation can enhance self-acceptance and self-efficacy. Skills gained in family psychoeducation can help the family deal with and possibly delay relapses.

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

Soo S, Zhang Z, Khong S, Low J, et al: Randomized controlled trials of psychoeducation modalities in the management of bipolar disorder: a systematic review. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17r11750. From the Institute of Mental Health, Singapore; and other institutions. **This review was conducted without direct funding. The authors declared no competing interests.**

*See Reference Guide.

Mitochondrial Agents for Bipolar Disorder

Therapies that target the mitochondria are of growing interest for the treatment of bipolar disorder. Evidence to support the emerging mitochondrial hypothesis of bipolar disorder includes an increased prevalence of mood disorders in patients with mitochondrial diseases and morphological abnormalities of mitochondria and abnormal energy metabolism in patients with bipolar disorder. Some already approved drugs for bipolar disorder—notably lithium, valproic acid, and atypical antipsychotics—improve mitochondrial function. According to a literature review, many other agents affect the function of the mitochondria, including supplements like N-acetylcysteine, coenzyme Q10 (CoQ10), alpha-lipoic acid, S-adenosyl methionine (SAME), melatonin, and a long list of vitamins. Most of these agents have plausible mechanisms of action involving the mitochondria, are well tolerated, and in some cases, have shown promise in preclinical and preliminary clinical studies. However, there is a need to develop novel candidate mitochondrial modulators and to conduct rigorous clinical trials.

Pereira C, Chavarria V, Vian J, Ashton M, et al: Mitochondrial agents for bipolar disorder. *International Journal of Neuropsychopharmacology* 2018; doi 10.1093/ijnp/pyy018. From the Centro Hospitalar Lisboa Norte, Lisbon, Portugal; and other institutions. **Source of funding not stated. Three of 7 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: ramelteon—*Rozerem*; valproate—*Depakene, Depakote*

Cognitive/Exposure Therapy for Hoarding Disorder

In a randomized trial, an exposure-based therapy was superior to intensive case management in treating hoarding disorder in older adults.

Background: Neurocognitive impairment may reduce the efficacy of standard cognitive behavioral therapy (CBT) for hoarding disorder in older adults. Cognitive Rehabilitation and Exposure/Sorting Therapy (CREST) is a manualized treatment developed and previously pilot-tested by the study authors. The treatment addresses neurocognitive weaknesses that may contribute to hoarding disorder while targeting the core symptoms of the disorder. It does not include cognitive restructuring or other elements of CBT. CREST consists of 26 weekly 40–60-minute individual sessions involving teaching such skills as cognitive flexibility and problem solving, exposure sessions in the clinic and the patient's home, and relapse prevention and maintenance. Patients receive daily homework assignments.

Methods: Study subjects, recruited from the community, were 58 adults aged ≥ 60 years (mean age, 67 years; 71% women) who met DSM-5 criteria for primary diagnosis of hoarding disorder. Participants were randomly assigned to receive either CREST or case management, which had similar intensity to CREST and was delivered by nurses who provided support, referral for needed medical and social services, and safety recommendations. Symptom

severity was assessed by blinded raters at baseline, 3 months (mid-treatment), 6 months (post-treatment), and 9 and 12 months. Primary outcome measures were the self-report Saving Inventory-Revised and the clinician-rated UCLA Hoarding Severity Scale (UHSS).

Results: More than 80% of CREST participants and 70% of the case-management group completed the 6-month post-treatment assessment. Patients in both treatment groups showed significant decreases in symptom severity from baseline to 6 months on all primary and secondary outcome measures. Symptom scores on the SI-R decreased by 38% in the CREST group, compared with 25% in the case-management group ($p=0.03$; effect size, $d^* 0.63$). Among the 3 SI-R subscales, CREST was associated with significantly greater improvement than case management in clutter ($p=0.022$), but not acquisition or difficulty discarding. Patients also showed improvement in the UHSS, favoring CREST numerically but not reaching statistical significance. Analysis of secondary outcomes showed that CREST was associated with larger mean percent improvement on the Activities of Daily Living–Hoarding scale (32% vs 13%; $p=0.035$); in anxiety on the Hospital Anxiety and Depression Scale (38% vs 14%; $p=0.04$); and on the Clinical Global Impression (CGI)–Severity Scale (27% vs 12%; $p=0.04$). More CREST participants met treatment response criteria on the CGI-Improvement scale (i.e., ratings of much or very much improved; 78% vs 28%; $p=0.001$). Additionally, more patients who received CREST achieved subclinical symptom status with odds ratios* ranging from 2.4 to 7.3 and numbers needed to treat* ranging from 2.6 to 4.5 depending on the symptom measure. Improvements in both treatment groups were stable through the 12-month follow-up interview.

Discussion: The efficacy of CREST may be due to its inclusion of compensatory cognitive training and emphasis on exposure therapy, rather than cognitive therapy. Case management may have improved multiple areas of patients' lives, allowing them to focus on addressing their hoarding problems. In the study, the frequency of sessions of case management, which is currently the most widely used intervention for hoarding disorder, was scheduled to match CREST and was much higher than is usually the case.

Ayers C, Dozier M, Twamley E, Saxena S, et al: Cognitive rehabilitation and exposure/sorting therapy (CREST) for hoarding disorder in older adults. *Journal of Clinical Psychiatry* 2018;79 (March/April):85-93. doi 10.4088/JCP.16m11072. From the VA San Diego Healthcare System, CA; and other institutions. **Funded by the VA. The authors declared no competing interests.**

*See Reference Guide.

rTMS for Comorbid Anxiety, Insomnia

In a pilot study, repetitive transcranial magnetic stimulation of the right parietal cortex had promising results in patients with comorbid generalized anxiety disorder (GAD) and insomnia.

Methods: Study participants, recruited from outpatient neurology clinics, met criteria for both GAD (DSM-IV-TR) and insomnia (DSM-IV) related to another mental disorder, with insomnia duration of ≥ 3 months. Patients were randomized to double-blind treatment with either low-frequency (1 Hz) rTMS administered over the right parietal cortex on 10 consecutive days or sham rTMS. The primary study outcome measure was the Hamilton Rating Scale for Anxiety (HAM-A). Responder status was defined as a $\geq 50\%$ improvement in the HAM-A score and remission as a score of < 8 . Secondary outcome measures were the Pittsburgh Sleep Quality Index and the Hamilton Rating Scale for Depression. Symptoms were assessed at baseline, immediately after the final treatment, and 2 weeks and 4 weeks after the end of treatment.

Results: A total of 36 patients were enrolled, and all completed the 10 days of treatment. Active rTMS was associated with a larger mean improvement in anxiety symptoms than sham rTMS at all evaluation points. The mean baseline HAM-A score was 20 in both treatment groups. Patients who received active treatment showed a significant 44% reduction in HAM-A score at

the post-treatment evaluation, while the sham group showed little change (8% reduction in score). At 1 month follow-up, 4 patients met remission criteria and an additional 6 met response criteria, compared with a single patient meeting response criteria in the sham group. Patients who received active treatment also had significant improvements in insomnia and depressive symptoms, while the sham group demonstrated no significant changes.

Discussion: The few previous studies of rTMS in GAD have targeted the right dorsolateral prefrontal cortex, with promising results. The choice of the right parietal cortex as a treatment target in the present study is based on the role of the parietal cortex in attention networks, which may bias attention toward threat-related stimuli. Functional MRI studies suggest these networks are abnormal in patients with GAD. rTMS may modulate the interaction between top-down attention and emotion processing, influencing both anxiety and insomnia.

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

Huang Z, Li Y, Bianchi M, Zhan S, et al: Repetitive transcranial magnetic stimulation of the right parietal cortex for comorbid generalized anxiety disorder and insomnia: a randomized, double-blind, sham-controlled pilot study. *Brain Stimulation* 2018; doi 10.1016/j.brs.2018.05.016. From Capital Medical University, Beijing, China; and other institutions. **Funded by the Natural Science Foundation of China; and other sources. 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 the treatment.

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

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

IMPORTANT REMINDER

Starting with the next issue, the delivery of *Psychiatry Alerts NOS* will be 100% electronic. Please note that our CME exams will be printed and mailed to you as usual.

If you have not yet done so, please register your email address with us by logging in to your account at www.alertpubs.com with your customer number (see envelope) and using the "Change Address" feature at the top of the page. If you don't have an online account, you can quickly and easily create one on the website. **And don't worry, we will never share your email address without your permission.**

If you need help accessing your monthly issues, email Donna at custservice@alertpubs.com or call her at 973-898-1200 between the hours of 9 AM and 3 PM EST weekdays.

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**
Founding Editor: **Michael J. Powers**

PSYCHIATRY ALERTS NOS

Binge Eating Disorder Treatments	47
Image-Focused Therapy in Bipolar Disorder	44
Ketogenic Diet for Mood Disorders	48
OCD: Combination Therapy.....	43
Peer Mentors and Rehospitalization	45
Psychosis Conversion Model.....	46
Reference Guide	48
TMS for OCD.....	43

Volume X / August 2018 / Number 8

www.alertpubs.com

Important Reminder . . . Delivery of *Psychiatry Alerts NOS* is now 100% electronic.

TMS Approved for OCD

The Brainsway Deep Transcranial Magnetic Stimulation System has received FDA approval for the treatment of obsessive-compulsive disorder not adequately responsive to medication, psychotherapy, or their combination. The Brainsway device is contraindicated in patients with metal objects or implanted stimulator devices in or near the head. These may include cochlear implants, deep brain stimulators, vagus nerve stimulators, aneurysm clips or coils, stents, and bullet fragments. During treatment with the device, patients are required to wear earplugs to reduce exposure to the loud sounds produced by the device, and jewelry and hair barrettes must be removed. Patients with a history of seizures should discuss this with their health care provider before receiving the treatment.

FDA New Release: FDA permits marketing of transcranial magnetic stimulation for treatment of obsessive compulsive disorder. Available at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm617244.htm>.

Combined Therapies for OCD

In a randomized trial, exposure and response prevention (ERP) combined with cognitive therapy (CT) was superior to a similar-intensity program of ERP alone in adult patients with obsessive-compulsive disorder.

Background: Comparative studies have shown ERP and CT to be similarly effective when used alone. However, ERP has been the most thoroughly investigated and is considered first-line treatment in international guidelines. The present study was conducted to determine whether adding elements of CT could improve the established efficacy of ERP.

Methods: Patients, recruited from a large community-based OCD clinic, met DSM-IV-TR criteria for OCD and had a score of >16 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Both treatment groups received individual, manualized ERP in 16 hour-long weekly sessions. ERP-only therapists avoided formal cognitive restructuring techniques, while the combined ERP-CT program used the exposure task to activate specific cognitive methods and targeted obsessive beliefs. Adherence to the separate treatment protocols and treatment

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5625) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Individual issues are available for \$10.00 each. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

integrity were monitored by blinded raters using audiotapes of sessions. The primary study outcome was change from baseline in Y-BOCS score.

Results: A total of 127 patients were randomized, and 94 completed treatment—42 in the ERP group and 52 in the ERP-CT group. Most study discontinuations were not attributed to study treatments. In an intent-to-treat analysis,* both treatments were associated with large improvements (effect sizes,* 1.27 for ERP and 1.89 for ERP-CT). The combined treatment was significantly more effective than ERP alone (between-group effect size, 0.61; $p < 0.005$). Both the obsessive and compulsive Y-BOCS subscales showed a larger improvement with ERP-CT than ERP alone (effect sizes, 0.53 and 0.63, respectively, for between-group difference; $p < 0.005$ for both subscales). Among patients who completed the study, 46% of the ERP group and 65% of the ERP-CT group were classified as responders, with a $\geq 30\%$ improvement in Clinical Global Impression (CGI) score ($p = 0.052$). Some 23% of the ERP group and 44% of the ERP-CT group reached mild-illness status, with a $\geq 50\%$ improvement on the CGI ($p < 0.01$). When patients were classified by their predominant symptom subtype (i.e., contamination/washing, doubting-harming/checking, symmetry/ordering, or pure obsessions/"bad thoughts"), no subtype responded preferentially to either treatment. The 2 therapies had equivalent effects on anxiety and depression. Among the 75% of treatment completers who were followed 6 months after treatment, the between-group difference was maintained.

Rector N, Richter M, Katz D, Leybman M: Does the addition of cognitive therapy to exposure and response prevention for obsessive compulsive disorder enhance clinical efficacy? A randomized controlled trial in a community setting. *British Journal of Clinical Psychology* 2018; doi 10.1111/bjc.12188. From Sunnybrook Health Sciences Centre, Toronto, Canada; and other institutions. **Funded by the Canadian Institutes of Health Research. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Image-Focused Therapy in Bipolar Disorder

In a preliminary study, an imagery-focused intervention reduced both anxiety symptoms and the duration of depressive episodes in patients with bipolar disorder.

Background: The study intervention—imagery-focused cognitive therapy (ImCT)—is based on the hypothesis that mental imagery might act as an "emotional amplifier", driving both mood instability and anxiety in bipolar disorder, as well as the frequent comorbidity of anxiety disorders with bipolar disorder and the role of imagery as a key cognitive mechanism for anxiety.

Methods: The present report is based on the first 11 patients to receive treatment with ImCT at the Oxford (U.K.) Mood Action Psychology Programme (OxMAPP). Patients with a diagnosis of bipolar disorder I, II, or NOS who were not currently experiencing mania were referred to the program by their psychiatrists, with whom they maintained contact for risk management and clinical care. All ImCT sessions were delivered by 2 co-therapists, to enhance a non-hierarchical, collaborative relationship with the patient. During a 4-session structured assessment, patients identified a primary imagery target that was distressing, amenable to treatment, and plausibly linked to their mood instability. The patient was then taught to use imagery rescripting, positive imagery, competing tasks, and meta-cognitive techniques. Treatment consisted of 3–8 hourly sessions as needed, followed by a flexible number of spaced follow-up sessions. Patients received a mean of about 6 treatment sessions and 5 follow-up sessions. Patients' mood was assessed weekly, online or via text message, using the Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR) and the Altman Self-Rating Scale for Mania (ASRM). Data were available for the 6 months preceding OxMAPP enrollment (baseline) to 6 months after the end of treatment.

Results: All 11 patients enrolled in the program completed treatment and follow-up. Nine of the 11 patients had a comorbid anxiety disorder, 5 were currently experiencing depression, and

10 were receiving pharmacotherapy. One patient provided no baseline data on mood. The remaining 10 patients had a small-to-medium reduction in depressive symptoms on the QIDS-SR from baseline to follow-up (effect size, * 0.38) and no change in ASRM mania symptoms. Duration of depressive episodes was significantly reduced from a mean of 4.6 weeks in the pre-treatment period to 0.85 weeks in the 6 months post-treatment ($p=0.02$). The number of depressive episodes was also reduced, but the difference did not reach statistical significance. Specifically, of the 7 patients who experienced a depressive episode during the baseline period, only 2 experienced a depressive relapse during follow-up and the duration was shorter. There were no changes in the number and duration of manic episodes. Patients experienced a large reduction (effect size, 2.82) in anxiety, evaluated with the Beck Anxiety Inventory, from baseline to 1 month after treatment completion.

Hales S, Di Simplicio M, Iyadurai L, Blackwell S, et al: Imagery-focused cognitive therapy (ImCT) for mood instability and anxiety in a small sample of patients with bipolar disorder: a pilot clinical audit. *Behavioral and Cognitive Psychotherapy* 2018; doi 10.1017/S1352465818000334. From the Oxford Institute of Clinical Psychology Training, U.K.; and other institutions. **Funded by the Wellcome Trust; the National Institute for Health Research; and other sources. Eight of 9 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

*See Reference Guide.

Peer Mentors in Serious Mental Illness

In a randomized trial, patients with serious mental illness who were assigned a peer mentor had a reduced rate of rehospitalization compared with those receiving standard care. Peer mentoring may be an effective, highly specific way to help difficult-to-engage patients.

Methods: For this study, recovery mentors (RMs) who self-identified as being in recovery from serious mental illness were hired from the community and trained to provide support to persons discharged from a psychiatric hospital. RMs were trained in recovery philosophy and promotion; local resources; personal boundary considerations/safety; and cultural competence, with a core emphasis on identifying patients' strengths and providing individualized support. RMs functioned independently of the mental health system and were encouraged to provide support based on their own experience. Study participants with a psychotic or mood disorder were discharged from an urban academic medical center, after multiple prior hospitalizations in the previous 18 months. At discharge, patients were randomly assigned to the RM program or to usual care. Participants could request an RM with a preferred demographic profile, illness, or personal history. RMs were introduced to patients within 1 week of study entry and offered services for up to 9 months after discharge, with weekly contact encouraged. Because this was an exploratory study, a number of outcomes were analyzed, with none considered primary and no correction for multiple comparisons.

Results: Of well over 4000 patients admitted to the hospital over 2 years, only 307 met the study's strict eligibility criteria. Of the 93 patients who consented to randomization, 15 withdrew from the study, and only 22 of the 48 patients assigned an RM ever met with their mentor. These 22 participants met with their RM an average of 13 times, for a mean of 25 hours in total.

Within the first discharge month, 15% of the RM group and 38% of the standard care group were readmitted. Individuals who met with their RM had a mean of 270 days to rehospitalization, compared with 135 days for the standard-care group ($p=0.03$). Readmission rates at 9-month follow up were 48% and 66% in the RM and standard groups, respectively. Patients who interacted with their RM also had less severe drug problems during follow-up and greater improvements in physical health, self-care, and social functioning. There were no treatment effects on other outcomes such as functional health, hope, service satisfaction, or sense of community.

Discussion: These findings suggest peer mentoring may be worthy of further study. However, these results may not be widely generalizable because of low enrollment. Furthermore, the patients who did not participate may be a unique subgroup that require a more assertive, specialized engagement effort. These results provided no information about whether the program's effectiveness was due merely to the attention of an interested person, or to spending time with a mentor with recovery experience.

O'Connell M, Sledge W, Staeheli M, Sells D, et al: Outcomes of a peer mentor intervention for persons with recurrent hospitalization. *Psychiatric Services* 2018;69 (July):760–767. From Yale University School of Medicine, New Haven, CT; and the VA Pittsburgh Healthcare System, PA. **Funded by Eli Lilly and Company; and other sources. The authors declared no competing interests.**

Predicting Conversion to Psychosis

A newly-developed model based on information obtained in an initial clinical interview has the potential to predict conversion to psychosis in clinical high-risk (CHR) individuals with nearly 75% accuracy.

Background: CHR is characterized by attenuated positive symptoms, and about one-third of CHR individuals convert to a psychotic disorder, usually within 2 years. In North America, CHR is identified mainly by the Structured Interview for Psychosis Risk-Syndromes (SIPS). The model described in the present study is based on clinical information and the SIPS questionnaire, including items suspected to be particularly informative but traditionally not scored by other research groups: violent ideation, violent behavior, and auditory and visual perceptual abnormalities.

Methods: Study participants were help-seeking individuals, aged 13–30 years, who were participating in an early detection and intervention program and met SIPS and DSM-5 criteria for CHR. All data used in developing the model were extracted from the baseline SIPS and the accompanying clinical interview. Over the next 2 years, participants were evaluated with the SIPS for conversion every 3 months or when conversion was suspected. The predictive model was developed and cross-validated within the same population.

Results: Of the 199 study participants (mean age, 20 years; 27% women), 64 (32%) converted to psychosis within the 2 years. Of 40 baseline variables evaluated, the model identified 17 factors that had predictive value for conversion to psychosis. After multiple cross-validation tests, 8 factors were most consistently associated with conversion. (See table.) Several other factors were also significant in the model: global assessment of functioning; perplexity and delusional mood; motor disturbance; suicidal ideation; history of sexual trauma; ideational richness; trouble with focus and attention; social functioning; and suicidal behavior. The risk score with the optimal combination of sensitivity and specificity* correctly identified 73% of converters and non-converters.

Discussion: The model had a moderately strong ability to discriminate between converters and non-converters, performing comparably with or better than the commonly used North American Prodrome Longitudinal Study (NAPLS) model. The primary advantage of this proposed model is that all of the

Model parameters predictive of conversion to psychosis	
Most consistent predictors	Standardized coefficient estimate (odds ratio)*
Visual perceptual abnormalities [†]	-0.43 (0.65)
Dysphoric mood [†]	-0.29 (0.74)
Unusual thought content	0.28 (1.32)
Disorganization	0.26 (1.30)
Violent ideation	0.26 (1.30)
Race (nonwhite)	0.24 (1.27)
Social anhedonia	0.23 (1.26)
Violent behavior	0.20 (1.22)

[†]Negative coefficients indicate an inverse association.

information can be obtained in a single, 1–2-hour interview. The model will be made available online as a "risk calculator" after it has been validated in other populations.

Ciarleglio A, Brucato G, Masucci M, Altschuler R, et al: A predictive model for conversion to psychosis in clinical high-risk patients. *Psychological Medicine* 2018; doi 10.1017/S003329171800171X. From Columbia University, New York, NY; and other institutions. **Funded by the NIH; and other sources. Three of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Treating Binge Eating Disorder

According to a systematic review and meta-analysis, there is moderate support for the efficacy of cognitive behavioral therapy (CBT) and guided self-help in binge eating disorder. Evidence that is modest at best supports a few other psychological treatments or medications. There is no evidence on the long-term effects of any treatment.

Methods: A literature search identified randomized controlled trials of any psychotherapy, pharmacotherapy, or combination in patients with DSM-IV or DSM-5 binge eating disorder, regardless of age or weight status. Studies with high risk of bias were excluded from the meta-analysis. Outcomes of interest included remission, eating disorder symptoms or behaviors, weight loss, quality of life, and adverse effects.

Results: Of 99 publications that met inclusion criteria, 45 were excluded because of high risk of bias—usually because of unclear randomization procedure, non-blinded raters, or high dropout rates. The remaining 45 studies included 17 placebo-controlled medication trials, 23 studies of a psychological therapy versus wait-list or another control condition, and 5 comparisons of a drug–psychotherapy combination versus placebo. All studies were conducted in adult patients, and most patients were women with concurrent overweight or obesity.

Studies were pooled for meta-analysis if they had similar treatment and control conditions. Results were reported as the risk ratio (RR)* or the standardized mean difference (SMD)*. CBT was supported with moderate evidence: 4 studies, mostly in women with a mean body mass index (BMI) of 37 and was effective for most of the outcomes evaluated. (See table.) None of the studies reported adverse effects.

Selected outcomes of meta-analysis of treatments for binge eating disorder		
Outcome	CBT vs wait list (RR or SMD)	CBT self-help vs wait list (RR or SMD)
Remission	RR, 0.40	RR, 0.25
Binge eating frequency	SMD, 0.83	SMD, 0.51
Eating disorder psychopathology	SMD, 0.50	SMD, 0.58
BMI	No difference	No difference
Depression	SMD, 0.42	SMD, 0.31

Other treatments had modest support, but only for limited outcomes. Interpersonal therapy, SSRIs, and lisdexamfetamine (*Vyvanse*) had modest effects on remission or reducing the frequency of binge eating. Lisdexamfetamine was the only treatment that reduced weight, and the effects were modest, with low-quality evidence.

None of the studies presented results separately for patients with and without obesity. The majority of studies did not report long-term follow-up. Few studies evaluated treatment effects on quality of life, an important concern in binge eating disorder.

Ghaderi A, Odeberg J, Gustafsson S, Rastam M, et al: Psychological, pharmacological, and combined treatments for binge eating disorder: a systematic review and meta-analysis. *PeerJ* 2018; doi 7717/peerj.5113. From the Karolinska Institute, Stockholm, Sweden; and other institutions. **Funded by the Swedish Agency for Health Technology Assessment, and Assessment of Social Services. The authors declared no competing interests.**

*See Reference Guide.

Ketogenic Diet for Mood Disorders

According to a literature review, despite a lack of clinical studies, the ketogenic diet appears to be a promising intervention meriting research in mood disorders, particularly in treatment-resistant presentations. The diet has potentially metabolic, neurotrophic, neuroprotective, and antiinflammatory effects that may improve the course of mood disorders, and it is well tolerated, although adherence can be challenging.

The ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that forces the body to use fats rather than carbohydrates as its main energy source. Fats are converted by the liver into ketones, which replace glucose as the main source of energy in the brain. The use of ketone bodies as fuel in the brain involves multiple enzymatic cascades with far-reaching effects, and ketone bodies are thought to be a more efficient source of energy than glucose. The diet also affects different monoamines including dopamine, noradrenaline, and serotonin. Effects on GABA and glutamate transmission may be important mechanisms underlying the anticonvulsant effects of this diet.

According to observational studies, the ketogenic diet has been effective in patients with epilepsy, and there have been reports of positive effects in schizophrenia and mood disorders. In animal models of depression, the ketogenic diet has had similar effects to antidepressant drugs. The potential for the ketogenic diet in treatment-resistant mood disorders rests in part on its metabolic effects. The diet reduces body weight and can help control obesity, insulin resistance, and metabolic syndrome, which are strongly correlated with treatment resistance in mood disorders. The diet also influences some of the mediators of treatment resistance: deprivation of brain-derived neurotrophic factor (BDNF), oxidative imbalances, and persistent, low-grade systemic inflammation. The diet increases BDNF in animals and has also been shown to have antioxidant and antiinflammatory effects.

Brietzke E, Mansur R, Subramaniapillai M, Martinez V, et al: Ketogenic diet as a metabolic therapy for mood disorders: evidence and developments. *Neuroscience and Behavioral Reviews* 2018; doi 10.1016/j.neubiorev.2018.07.020. From the University of Toronto, Canada; and other institutions. **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.

Intent-to-Treat Analysis (ITT): An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an ITT analysis, everyone who begins treatment is included regardless of treatment completion.

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.

Risk Ratio: 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.

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.

Standardized Mean Difference: The difference between 2 normalized means—i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales, a value of 0 to 0.2 is considered a negligible effect, 0.2 to 0.5 a small effect, 0.5 to 0.8 a medium effect, and >0.8 a large effect.

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**
Founding Editor: **Michael J. Powers**

PSYCHIATRY ALERTS NOS

Adjunctive VNS in Depression.....	51
Biological Aging and Depression.....	52
Reference Guide.....	54
Self-Injury: Online Self-Help.....	51
Smartphone Apps for Mental Health.....	53
Substance Abuse and Bipolar Recovery	49
Suicide Risk Factors in Bipolar Disorder.....	50

Volume X / September 2018 / Number 9

www.alertpubs.com

Important Reminder . . . Delivery of *Psychiatry Alerts NOS* is now 100% electronic.

Substance Abuse and Bipolar Disorder Recovery

In a psychosocial-treatment trial, patients with bipolar disorder and a comorbid substance use disorder were significantly more likely to recover from depression within 1 year and to recover more rapidly than patients without a substance use disorder.

Methods: This study was a post-hoc analysis of data from a randomized treatment trial conducted within the large multicenter observational Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. The analysis included patients who participated in a randomized trial, nested within STEP-BD, comparing 30 sessions of intensive psychotherapy (over 9 months) with a brief, psychoeducation-based collaborative care intervention. The aim of the analysis was to examine the effect of substance use disorders on the likelihood of recovery or time to recovery. Study subjects had bipolar I or II disorder and a current major depressive episode and were allowed to participate if they had a past alcohol or drug use or dependence disorder or a current disorder that did not require immediate treatment. Recovery—defined as ≥ 8 consecutive weeks with ≤ 2 DSM-IV depressive, manic, or hypomanic symptoms—was evaluated over ≤ 1 year of follow-up.

Results: Of the 270 study participants, about 55% had a lifetime substance use disorder and 17% had a current disorder; 13% had a current alcohol use disorder and 8% a current drug use disorder. In this sample, intensive psychotherapy was associated with a significantly greater likelihood of recovery (odds ratio,* 1.66; $p=0.04$) and a more rapid time to recovery (odds ratio, 1.42; $p=0.03$) than collaborative care.

Patients with a current substance use disorder had a 2-fold higher likelihood of recovery than those without a current disorder ($p=0.05$), as well as a more rapid onset of recovery ($p=0.01$). Both drug and alcohol disorders, if current, were associated with improved recovery. Past substance use disorders were not associated with either outcome. Neither current nor past substance use disorders influenced patients' differential response to intensive psychotherapy versus collaborative therapy.

Discussion: This study is unique in allowing patients with concomitant substance use disorders to participate in a randomized treatment trial, and the results were contrary to the investigators'

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5625) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Individual issues are available for \$10.00 each. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

expectation that current substance use disorder would negatively impact recovery. Previous naturalistic observations of the STEP-BD cohort suggested that substance use disorders had a negative effect on recovery, or that they had no effect on recovery but increased the likelihood of a manic switch. A potential explanation for the present finding is a bias from the exclusion of patients with urgent substance problems.

Gold A, Peters A, Otto M, Sylvia L, et al: The impact of substance use disorders on recovery from bipolar depression: results from the Systematic Treatment Enhancement Program for Bipolar Disorder psychosocial treatment trial. *Australian & New Zealand Journal of Psychiatry* 2018; doi 10.1177/0004867418788172. From Boston University, MA; and other institutions. **STEP-BD is funded by the NIMH. Research described in this article was funded by the Dauten Family Center for Bipolar Treatment Innovation; and other sources. Seven of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Suicide Risk Factors in Bipolar Disorder

A Swedish population-based study identified a range of general, disorder-specific, and gender-specific risk factors for completed suicide in patients with bipolar disorder. Although this knowledge is valuable, suicide prevention efforts should not be based solely on risk factors.

Methods: The cohort consisted of patients enrolled in the Swedish National Quality Register for Bipolar Affective Disorder (BipolÄR) between 2004 and 2013. All patients with bipolar disorder who received treatment at psychiatric outpatient clinics in Sweden are offered registration. The register captures data collected by psychiatrists and staff in the course of clinical care and contains detailed information on sociodemographic factors, clinical history, family history, criminal convictions, and more. The study outcome was suicide, registered in Sweden's Cause of Death Register.

Results: The cohort consisted of 12,850 persons with bipolar disorder (62% women) who were followed for a median of 3.8 years. Within the cohort, there were 90 completed suicides, 55 in men and 35 in women. Identified risk factors for completed suicide included: male gender (hazard ratio [HR],* 2.56); living alone (HR, 2.45); criminal conviction in the previous year (HR, 4.43); history of an affective episode in the previous year (HR, 2.39); depressive episode in the previous year (HR, 2.24); any comorbid psychiatric disorder (HR, 2.64); previous suicide attempt (HR, 4.1); inpatient psychiatric care in the previous year (HR, 2.79); and involuntary psychiatric hospitalization in the previous year (HR, 3.5). All associations were statistically significant ($p < 0.01$ for all). Among comorbid psychiatric illnesses, risk of suicide was significantly increased with substance use (HR, 3.79), anxiety (HR, 1.91), and personality disorders (HR, 2.49), but not with eating disorders. Suicide was somewhat less frequent in patients with bipolar II disorder than type I, but the difference was not statistically significant. When data for men and women were analyzed separately, living alone, substance use disorder, involuntary commitment, and a recent affective episode were significant risk factors in men but not in women. Criminal conviction, comorbid personality disorder, and a recent depressive episode were significant predictors in women but not in men.

Discussion: It should be noted that as the registry included only Swedish patients, the results may not be generalizable to all populations. In addition, several other previously identified risk factors for suicide (e.g., early life adversity, family history of suicide, physical comorbidity, polarity of initial episode, total number of lifetime episodes, presence of psychotic features) were not captured in the registry.

Hansson C, Joas E, Pålsson E, Hawton K, et al: Risk factors for suicide in bipolar disorder: a cohort study of 12 850 patients. *Acta Psychiatrica Scandinavica* 2018; doi 10.1111/acps.12946. From the University of Gothenburg, Sweden; and other institutions. **Funded by the Swedish Research Council; and other sources. The authors declared no competing interests.**

*See Reference Guide.

Online Self-Help for Nonsuicidal Self-Injury

In a randomized trial of adults with nonsuicidal self-injury (NSSI), online interventions involving brief daily writing tasks reduced self-criticism, NSSI episodes, suicidal ideation, and depressive symptoms. The study's experimental treatment—Autobiographical Self-Enhancement Training (ASET)—had effects similar to another active control intervention and to a third control intervention that was intended to be inactive.

Methods: Participants were recruited from online forums related to self-injury and severe psychopathology. To enter the study, users were required to be aged ≥ 18 years and to have had ≥ 2 self-reported episodes of NSSI in the past month. The 3 randomly assigned treatments each involved a 5-minute daily writing assignment. The ASET assignment consisted of writing about something that made the participant feel good as a person. The active control, expressive writing, consisted of writing about something that bothered or concerned the individual. Journaling, the inactive control, consisted of simply recording the events of the day. Participants used anonymous email addresses and had no in-person contact with study personnel. They were emailed daily reminders and were paid for each completed assignment and weekly assessment. The primary study outcomes of self-reported episodes of NSSI and self-criticism, measured with the Self-Rating Scale, were evaluated online at the end of the 28-day interventions and again 4 weeks later.

Results: The sample consisted of 144 individuals (85% women), with a mean age of 26 years. The majority of patients had received psychiatric treatment, and about half were currently receiving treatment, 46% with medication. All patients completed ≥ 1 writing assignment, 77% completed >21 , and 81% completed all follow-up assessments.

Regardless of treatment group, participants showed significant reductions in self-criticism ($p < 0.001$) and in NSSI episodes ($p = 0.02$). They also showed significant decreases in depression measured with the Beck Depression Inventory ($p < 0.001$) and in suicidal ideation ($p = 0.02$). Desire to discontinue NSSI, likelihood of future NSSI, suicidal plans, and suicidal behaviors all remained unchanged. There were few differences in outcomes between groups and they were not maintained at the 3-month follow-up, with the exception that ASET was associated with significantly fewer days of suicidal ideation compared with expressive writing ($p = 0.048$). In a post-study evaluation, patients in the ASET group said that they found the writing assignments less enjoyable and more annoying than patients in either the expressive writing or journaling groups.

Discussion: All of the treatments provided clinical benefits and reduced episodes of NSSI. However, levels of self-criticism remained high, reductions did not persist after the end of treatment, and many outcomes were unaffected. The benefits of journaling were unexpected. All 3 writing interventions appear to warrant further investigation as highly scalable and easily disseminated treatments.

Hooley J, Fox K, Wang S, Kwashie A: Novel online daily diary interventions for nonsuicidal self-injury: a randomized controlled trial. *BMC Psychiatry* 2018; doi 10.1186/s12888-018-1840-6. From Harvard University, Cambridge, MA. Funded by the Eric M. Mindich Research Fund for the Foundations of Human Behavior. The authors declared no competing interests.

Adjunctive VNS and Quality of Life in Depression

Vagus nerve stimulation is FDA approved as adjunctive treatment for resistant major depression. According to a longitudinal analysis of a registry of patients who received treatment for resistant depression, adjunctive VNS is also associated with clinically significant improvement in quality of life, persisting over 5 years of observation.

Methods: The 5-year registry enrolled patients with unipolar or bipolar depression, resistant to ≥ 4 antidepressant trials. All patients received treatment naturalistically with medication,

psychotherapy, and/or ECT or other neurostimulation. About half of the sample received adjunctive VNS. Follow-up evaluations were conducted every 3 months for the first year, and then at 6-month intervals. Quality of life was assessed with the Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF), a 14-item self-report instrument scored from 14 to 70, with higher scores indicating a better quality of life. Depression was assessed with the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: The sample consisted of 271 patients receiving treatment as usual and 328 receiving adjunctive VNS. About one-fourth of patients had bipolar disorder; patients had a mean lifetime total of nearly 8 failed treatments and an average of nearly 2 suicide attempts. Average baseline Q-LES-Q scores were about 15% of the maximum possible.

Patients who received VNS had greater improvement in the Q-LES-Q than the control group, beginning 3 months after the start of treatment and lasting through the entire 5 years of observation. The effect of VNS was additive over the range of MADRS improvement, so that patients who received VNS had a mean Q-LES-Q improvement of 4 points compared with treatment-as-usual patients who experienced the same drop in the MADRS score. The effect was observed in patients with unipolar depression and in those with bipolar disorder, although the latter group was not large enough to demonstrate statistical significance. Previous research identified a Q-LES-Q increase of 11.89% as the minimal clinically important difference. In the present study, this level of improvement was reached by patients in the VNS group who had a $\geq 34\%$ decrease from baseline in MADRS score, lower than the $\geq 50\%$ decrease that typically defines treatment response. Patients in the treatment-as-usual group had a comparable Q-LES-Q improvement after achieving a $\geq 56\%$ improvement in MADRS score. VNS was associated with an improved likelihood of achieving clinician-rated response, as measured by a Clinical Global Impression–Improvement rating of much or very much improved (odds ratio,* 2.78). Of the individual domains measured by the Q-LES-Q, VNS was associated with greater improvements than control in mood, household activities, leisure activity, ability to function, overall well-being, social relationships, family relationships, and sex drive. Treatment-as-usual patients had better economic status; the groups had similar results for the remaining 4 domains.

Discussion: These findings are potentially important because patients in this highly refractory group are unlikely to experience response to additional medications. The positive results of the present study suggest that randomized controlled trials to evaluate quality-of-life effects of adjunctive VNS in this difficult-to-treat population are warranted.

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

*See Reference Guide.

Biological Aging in Depression

A Dutch cohort study found epigenetic aging, an indicator of biological aging, was advanced in individuals with depression compared with a group of healthy subjects. The accelerated biological aging in these patients may contribute to the increased risk for mortality and aging-related diseases observed in patients with depression.

Methods: DNA methylation provides a marker of biological age (DNAm age) that can be compared with an individual's biological age. The present study compared DNAm age estimates in participants in the Netherlands Study of Depression and Anxiety longitudinal cohort study. For this analysis, the investigators selected a subset of the cohort who had current or lifetime major depressive disorder, with a score of ≥ 14 on the Inventory of Depressive

Symptomatology (IDS), and a control group with current IDS scores <14 and no lifetime psychiatric disorders. DNA methylation was assessed using blood samples, and age estimation was based on chronological ages of the full study group (n=811) and of only control subjects (n=319). The DNAm age analysis was replicated in postmortem brain samples from 4 different U.S. and European brain banks.

Results: The mean chronological age of both groups was 41.5 years. According to epigenetic aging estimates, patients with depression were an average of 0.64 years, or 7.7 months, older than controls (p=0.008) after adjustment for a wide array of covariates. Greater epigenetic aging was associated with higher scores on the IDS in the overall sample (p=0.001). Epigenetic aging was also associated with higher scores on a Dutch structured inventory of childhood trauma (p=0.001). Depression severity was also correlated with childhood trauma (p<0.001), which makes it difficult to discern which of these 2 factors accounts for increased epigenetic aging. Aging was not associated with clinical characteristics of depression, including age at onset, illness duration, or medication use. These findings were replicated in postmortem brain samples from 74 persons with depression and 67 controls, matched for chronological age and gender. The depression group was estimated to be on average 1.11 years older by DNAm than the control group (p=0.03).

Discussion: Epigenetic aging has been linked with many physical illnesses and behavioral risk factors, but associations with life stressors and mental illnesses such as schizophrenia have been mixed. The present observations indicate that advanced aging is present in both the blood and brain of patients with depression, suggesting that at least some processes that affect epigenetic aging are active in both tissues. Because the study was cross-sectional, it was not possible to discover whether accelerated epigenetic aging occurs before adulthood, possibly as a consequence of childhood trauma, or whether greater epigenetic aging occurs throughout life.

Han L, Aghajani M, Clark S, Chan R, et al: Epigenetic aging in major depressive disorder. *American Journal of Psychiatry* 2018;175 (August):774–782. doi 10.1176/appi.ajp.2018.17060595. From the VU University Medical Center, the Netherlands; and other institutions. **Funded by the Netherlands Organization for Health Research and Development; the NIMH; and other sources. One of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Smartphone Apps for Mental Health

Use of mental health smartphone apps significantly improved well-being in a nonclinical population. Two of the 3 evaluated apps were associated with reductions in depressive symptoms, but no app reduced anxiety symptoms.

Background: Mental health apps may be most useful in preventive and stepped-care approaches to emotional problems. However, previous studies and meta-analyses have relied on clinical samples, programs that require clinician-delivered feedback, and programs that are not available to the public. The present study is notable for being conducted in a nonclinical population using generally available programs, for examining effects on positive well-being, and for exploring mechanisms that may mediate the effects of the apps.

Methods: The study compared the effects of MoodPrism, MoodMission, and MoodKit, all self-guided CBT-based apps that use different therapeutic techniques. Participants were recruited using social media, and were then randomly assigned to 1 of the apps or to a wait-list control condition. The 3 apps were available from the Australian iOS and Android app stores, either without cost or using free access provided by the study. Efficacy outcomes were: depression symptoms, measured with the Patient Health Questionnaire-9 (PHQ-9); anxiety symptoms, measured with the 7-item Generalized Anxiety Disorder Scale (GAD-7); and mental wellbeing, measured with the Warwick-Edinburgh Mental Well-being Scale (WEMWBS). Outcomes were assessed using these measures via email link, with the final assessment after 30 days.

The apps include features that may increase emotional self-awareness (particularly MoodPrism and MoodKit), coping self-efficacy (particularly MoodMission and MoodKit), and mental health literacy (all 3 programs). Each of these 3 intermediate outcomes was examined as a potential mediator of the ultimate treatment effects.

Results: Study participants (n=226) had a mean age of 34 years, 81% were women, and 141 completed the 30-day assessment. At baseline, 55% of subjects had PHQ-9 scores indicating a likely depression diagnosis, and 36% had GAD-7 scores indicating a likely anxiety disorder.

Compared with the waitlist control group, participants who used any active intervention showed improvement in mental well-being, and users of MoodKit and MoodMission had reductions in depressive symptoms. (See table.) All active treatments were associated with increases in coping self-efficacy, which was shown to mediate the positive effects of MoodKit and MoodMission. Changes in emotional self-awareness and mental health literacy were small and did not mediate the mental health outcomes.

Effects of 3 smartphone apps on depression, anxiety, and mental wellbeing					
Outcome	Intervention	Change from baseline		Difference from control	
		Effect size [†]	Significance	Effect size [†]	Significance
Depression (PHQ-9)	Control	0.069	p<0.05	—	—
	MoodKit	0.341	p<0.001	0.035	p<0.05
	MoodPrism	0.237	p<0.001	0.007	NS
	MoodMission	0.318	p<0.001	0.038	p<0.05
Anxiety (GAD-7)	Control	0.020	NS	—	—
	MoodKit	0.153	p<0.01	0.017	NS
	MoodPrism	0.136	p<0.01	0.009	NS
	MoodMission	0.146	p<0.01	0.017	NS
Well-being (WEMWBS)	Control	0.066	p<0.05	—	—
	MoodKit	0.438	p<0.001	0.074	p<0.01
	MoodPrism	0.392	p<0.001	0.037	p<0.05
	MoodMission	0.558	p<0.001	0.089	p<0.001

[†]Using the partial eta-squared statistic; see Reference Guide

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

Bakker D, Kazantzis N, Rickwood D, Rickard N: A randomized controlled trial of three smartphone apps for enhancing public mental health. *Behaviour Research and Therapy* 2018;109:75–83. doi 10.1016/j.brat.2018.08.003. From Monash University, Australia; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Reference Guide

Effect Size (Partial Eta-Squared): The effect size represents the amount of change in outcome that can be attributed to treatment, when using the partial eta squared statistic, 0.01 indicates a small effect, 0.06 a medium effect, and 0.14 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.

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).

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
 Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
 Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**
 Founding Editor: **Michael J. Powers**

PSYCHIATRY ALERTS NOS

CBT plus Biofeedback for PTSD.....	58
Habenular Connectivity in Depression	59
OCD: Concentrated Treatment.....	55
Reference Guide	60
rTMS in Pregnancy.....	57
Traumatic Brain Injury and Suicide Risk	56

Volume X / October 2018 / Number 10

www.alertpubs.com

Important Reminder . . . Delivery of *Psychiatry Alerts NOS* is now 100% electronic.

Highly Concentrated Treatment of OCD

In a naturalistic treatment study, a highly accelerated 4-day exposure and response prevention (ERP) protocol was both feasible and effective in a group of patients with OCD. The results suggest that concentrated therapy has low attrition rates and is at least as effective as longer-term therapy.

Background: In Norway, all patients with OCD are given access to empirically supported treatment by a specialized OCD team. When an unexpected number applied for treatment at Oslo University Hospital, the waiting list grew to 101 patients. In an effort to clear the waitlist, a single clinic employed the Bergen 4-day treatment protocol in 90 consecutive patients over 2 weeks. The accelerated treatment is based on psychoeducation with exposure and response prevention (ERP) and individual treatment in a group setting, with a patient-to-therapist ratio of 1:1 within small groups.

Methods: Study participation criteria were broad: Patients received treatment if they met DSM-5 criteria for OCD, had moderate-to-severe symptoms, and were free of suicidality, psychosis, and substance abuse. Of the 101 waitlisted patients, 11 were excluded for practical reasons or because they did not meet study criteria. Of the remaining 90 patients, all agreed to participate in the accelerated treatment program. Patients were assigned to 1 of 2 cohorts, each consisting of 8 groups of 6 patients; 66 therapists delivered treatment. Therapists met for 8 hours of training on Monday, and sessions with patients were scheduled for the following 4 weekdays. Treatment consisted of a 3-hour day of psychoeducation, followed by 2 days (8–10 hours each) of therapist-assisted individual exposure training and brief group meeting, and a final day of review and planning. An educational meeting for family and friends was also included on day 4. Patients were encouraged to continue with self-administered exposures for the next 3 weeks and to report their experiences daily online. Outcomes were measured after the 4-day treatment and 3 months later. Clinically relevant response was defined as a $\geq 35\%$ reduction in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score, and remission was defined as a post-treatment Y-BOCS score of ≤ 12 .

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5641) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Individual issues are available for \$10.00 each. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

Results: All 90 patients completed the study treatment, and overall, patients experienced a significant reduction in the Y-BOCS score, from a pre-treatment mean of 26 to 10.5 after completing the 4-day protocol ($p < 0.001$; effect size, * 4.6). At the end of treatment, 91% of the patients met response criteria and 72% had achieved remission. At the 3-month follow-up, the mean Y-BOCS score remained stable at 10.7 ($p < 0.001$; effect size, 4.6), 84% of patients were considered responders, and 68% achieved remission. Of 8 patients who were classified as unchanged after treatment, 4 had achieved remission by the 3-month follow-up. Results did not differ in subgroup analysis of patients with moderate or severe symptoms.

Discussion: The results of this study are similar to previously reported results of the 4-day protocol and are somewhat better than those generally reported for standard ERP treatments. The format is likely to be highly cost-effective, and the 100% completion rate suggests it is acceptable to patients.

Kvale G, Hansen B, Björgevinnson T, Børtveit T, et al: Successfully treating 90 patients with obsessive compulsive disorder in eight days: the Bergen 4-day treatment. *BMC Psychiatry* 2018; doi 10.1186/s12888-018-1887-4. From Haukeland University Hospital, Bergen; and the Norwegian University of Science and Technology, Trondheim, Norway. **Source of funding not stated. The authors declared no competing interests.**

*See Reference Guide.

Traumatic Brain Injury and Suicide Risk

According to the results of a Danish population-based study, persons with a history of traumatic brain injury (TBI) have twice the risk of suicide as the general population without TBI.¹ Suicide risk was increased across all severity levels of TBI, including mild injuries. The research also identified an important clinical triad that serves as a "red flag" for increased suicide risk: a history of TBI, recent injury (especially with long hospital stays), and multiple post-injury medical contacts for the injury.

Methods: The study cohort consisted of all individuals aged ≥ 10 years who lived in Denmark beginning January 1, 1980. Through the end of follow-up in 2014, information on medical contacts for TBI, deaths by suicide, and covariates were obtained from linked registries. TBI was categorized as: mild (concussion); skull fracture without documented TBI; or severe (head injury with evidence of structural brain injury).

Results: The dataset included >7.4-million persons, of whom 5.7% had experienced a mild TBI, 0.3% had a skull fracture, and 1.6% had a severe TBI. More than 34,500 suicides occurred, 10.2% of them in persons with a history of TBI.

The absolute rate of suicide in persons with TBI was about twice that of the population with no TBI. (See table.) Risk of suicide increased with increasing TBI severity. A higher suicide rate was associated with an increasing number of medical contacts for likely distinct TBI events ($p < 0.001$ for trend). Suicide rates were also increased as a function of the number of days in treatment for TBI ($p < 0.001$ for trend) and of recency of contact; suicide risk was highest within the first 6 months after the injury. Suicide rates were elevated in all age groups of TBI patients, but particularly in persons between the ages of 16 and 20 years. Also contributing to

Incidence of suicide in relation to TBI history and severity		
Group	Absolute rate per 100,000 person-years	Incidence rate ratio*
No TBI	19.9	reference
Any TBI	40.6	1.90
Mild TBI	38.6	1.81
Skull fracture	42.4	2.01
Severe TBI	50.8	2.38

suicide risk were the onset of a psychiatric disorder after the TBI and engaging in deliberate self-harm after the injury.

Editorial.² TBI is a known risk factor for suicide, but only recently have the consequences of mild TBI received recognition. Mild TBI is by far more common than severe TBI and may be associated with depression and impulsivity. There is increasing awareness of chronic traumatic encephalopathy in victims of repetitive head injuries from contact sports and in military veterans with blast exposure, and of lasting brain abnormalities, cognitive deficits, and neuropsychiatric disturbances in persons with mild TBI.

¹Madsen T, Erlangsen A, Orlovskaya S, Mofaddly R, et al: Association between traumatic brain injury and risk of suicide. *JAMA* 2018;320 (August 14):580–588. doi 10.1001/jama.2018.10211. From the Danish Research Institute of Suicide Prevention, Copenhagen, Denmark; and other institutions. **Funded by the Mental Health Services Capital Region Denmark; and other sources. One study author disclosed a potentially relevant financial relationship; the remaining 5 authors declared no competing interests.**

²Goldstein L, Diaz-Arrastia R: Traumatic brain injury and risk of suicide [editorial]. *JAMA* 2018;320 (August 14):554–556. From Boston University School of Medicine, MA; and other institutions. **The authors declared no competing interests.**

*See Reference Guide.

rTMS During Pregnancy

In a small controlled trial, repetitive transcranial magnetic stimulation reduced depressive symptoms in women treated in the 2nd or 3rd trimester of pregnancy. Treatment produced few maternal adverse effects and did not appear to affect fetal outcomes; however, there were 3 late preterm births in the active rTMS group, a finding of uncertain significance.

Methods: Study participants were required to be between the ages of 18 and 39 years, 14–34 weeks pregnant, and to have a diagnosis of unipolar major depressive disorder. Also required were minimum scores of 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D) and 3 on the Clinical Global Impression–Severity* (CGI-S) scale. Antidepressant medication was permitted if the dose was stable for 2 weeks before randomization, and women with comorbid anxiety disorder were allowed to enroll. Patients received a total of 20 sessions of active or sham rTMS, administered 5 days per week and targeting the right dorsolateral prefrontal cortex. Primary study outcomes, assessed at the end of treatment, were change from baseline in HAM-D and CGI-S scores.

Results: Of 26 women randomly assigned to treatment, 22 completed ≥ 17 sessions and 20 completed all 20 sessions. Women who withdrew early did so for reasons unrelated to treatment. During the study, 5 women received pharmacotherapy and 4, all in the control group, had a comorbid anxiety disorder.

At study entry, mean HAM-D and CGI-S scores (23 and 4.6, respectively) did not differ between the active rTMS and sham groups. Women who received active rTMS had larger decreases in depressive symptoms and clinical severity than those who received sham treatment. (See table.)

Outcomes of real vs sham rTMS during pregnancy			
Outcome	Active treatment	Sham	Significance
Mean Final HAM-D Score	9.27	13.18	p=0.003
Mean Final CGI-S Score	2.36	3.18	p=0.035
Mean Final EPDS Score	9.55	13.00	p=0.008
Response	82%	45%	p=NS
Remission	27%	18%	P=NS

The number needed to treat* for 1 additional response was 3. Rates of response ($\geq 50\%$ decrease in HAM-D score) and remission (final HAM-D score < 8 and CGI-S score ≤ 1) were numerically, but not significantly, higher with active treatment, possibly because of the small sample size. There were also no significant differences between the groups in patient-rated Beck Depression Inventory and Beck Anxiety Inventory change. Postnatal mean scores on the Edinburgh Postnatal Depression Scale (EPDS) were lower in patients receiving active treatment, but in telephone interviews at 6 weeks, scores did not differ between the groups.

No treatment-related changes in estradiol or progesterone levels were observed, nor were there any clinically relevant cognitive changes. rTMS was associated with few maternal adverse effects other than the expected transient headaches. Fetal growth did not differ between the groups, and there were no significant differences in fetal age at delivery. However, 3 infants in the rTMS group were delivered in gestational weeks 35 or 36. Pre-term birth risk factors unrelated to TMS were present in 2 of these mothers.

Discussion: The high treatment adherence in this study may indicate women's desire for effective alternatives to medication during pregnancy. Patients received right-sided rTMS in this study because of concerns, later shown to be unfounded, that left-sided treatment increases seizure risk. It is likely, although unproven, that left-sided rTMS is equally safe in pregnancy and more effective than right-sided treatment. The dosage of rTMS used in the present study was also conservative, only half the dose considered safe in the general patient population. Larger studies in more varied populations appear to be warranted.

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

Kim D, Wang E, McGeehan B, Snell J, et al: Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder. *Brain Stimulation* 2018; doi 10.1016/j.brs.2018.09.005. From Perelman School of Medicine at the University of Pennsylvania, Philadelphia. **Funded by the NIMH. One of the 9 study authors disclosed a potentially relevant financial relationship; the remaining authors declared no competing interests.**

*See Reference Guide.

CBT with Heart Rate Variability Biofeedback for PTSD

In an uncontrolled study, patients with noncombat-related PTSD experienced significant benefit from cognitive behavioral therapy with heart rate variability biofeedback.

Methods: Study participants were 30 adults (mean age, 44 years; 22 women) referred for non-combat PTSD treatment. Participants had a wide range of co-occurring conditions, including suicidal ideation and substance abuse, and nearly all had experienced their trauma > 10 years in the past, mostly as childhood physical/emotional or sexual abuse. All treatment was provided by a single clinician, who also rated the results. The therapy was organized into distinct modules that taught basic core skills or addressed common PTSD symptoms—i.e., nightmares, dissociation, hyperarousal and reactivity, avoidance, and negative conditions and moods. The initial session included nonspecific practice in distress tolerance, physiological calming, and self-soothing. After completing 2–3 sessions of initial evaluation, patients only used the modules that were most relevant to their symptom profile, completing treatment after a total of 6–14 sessions.

Heart rate variability biofeedback was used as part of the hyperarousal and reactivity module. In the clinic, patients wore a sensor on an earlobe or finger, and heart rate variability was displayed on a computer monitor. They were able to view their heart rate response to skills they were learning, such as paced diaphragmatic breathing. Patients practiced these skills between sessions and were able to test themselves when they returned to the clinic. They were encouraged to practice breathing skills every day to reduce hyperarousal and reactivity.

PTSD symptoms were measured following treatment using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), past-month version, including the Life Events Scale-5. The primary outcome of this observational study was remission, defined as no longer meeting CAPS-5 diagnostic criteria for PTSD.

Results: Of the 30 enrolled patients, 26 completed the protocol and achieved remission of PTSD. In the intent-to-treat analysis,* the remission rate was 87%. Treatment completers experienced an average 43% reduction in CAPS score. The average Clinical Global Impression-Improvement* score was 1.69. A total of 25 patients were reevaluated after 3 months; only 1 patient reported a return of symptoms, which were relatively mild.

Discussion: The remission rate in this study, admittedly a biased estimate, compares favorably with other published reports and meta-analyses of PTSD treatment. The protocol could be easily administered by a range of mental health clinicians and appears to be applicable to patients with persistent PTSD and complex co-occurring issues. However, the positive results require replication in higher quality studies.

Criswell S, Sherman R, Krippner S: Cognitive behavioral therapy with heart rate variability biofeedback for adults with persistent noncombat-related posttraumatic stress disorder. *The Permanente Journal* 2018; doi 10.7812/TPP/17-207. From Kaiser Permanente Northwest, Portland, OR; and other institutions. **This study was not funded. The authors declared no competing interests.**

*See Reference Guide.

Habenular Connectivity and Depression Response

The habenula is a small brain structure that interfaces with the basal ganglia and limbic system, influencing multiple neurotransmitter systems with potential effects on motivational and emotional control of behavior. In a large sample of psychiatric inpatients, MRI studies of structural and functional habenular connectivity on admission were predictive of response to treatment for depression.

Methods: Study subjects were consecutively admitted to a psychiatric hospital, where treatment consisted of medication, individual and group psychotherapy, nursing care, health promotion, exercise, and recreation. The typical duration of hospitalization was 4–8 weeks. More than 800 patients, regardless of diagnosis, were invited to volunteer for an MRI study. The sample for the present analysis consisted of 175 patients with scans obtained upon admission and with baseline diagnoses of at least moderately severe depression, defined as a Patient Health Questionnaire depression module (PHQ-9) score of ≥ 15 . Participants were classified as responders or nonresponders based on their discharge PHQ scores, with 127 exhibiting mild or no depression (PHQ-9 score < 10) and 48 with at least moderate depression.

Neuroimaging data were extensively modeled to localize the habenula and its connecting tracts to previously described regions of interest. These regions, located downstream of the habenula, were selected based on their known connectivity with the habenula, role in neurotransmitter regulation, and proposed involvement in depression: the dorsal raphe, locus ceruleus, median raphe, substantia nigra, and ventral tegmental area.

Results: The scans identified an overall significant difference in habenular connectivity between responders and nonresponders ($p=0.00016$). Nonresponders had higher functional connectivity of the left habenula to the locus ceruleus ($p=0.003$) and lower structural and functional connectivity of the right habenula to the median raphe ($p=0.011$) and the right habenular afferent fibers ($p=0.025$). No other significant differences between groups were observed. No differences in connectivity between groups were observed for major depression, alcohol dependence, or eating disorder NOS, baseline diagnoses that differed in frequency between

responders and nonresponders. Differences in habenular connectivity explained 28% of the variance in treatment resistance and correctly classified 73% of the patients as responders or nonresponders.

Discussion: The habenula connects with brain regions associated with the dopaminergic, serotonergic, and noradrenergic neurotransmitter systems. The present research suggests studies of habenular connectivity could help identify patients who may require more extreme interventions for depression. The results also support some hypotheses about the pathophysiology of depression. Apparently the dorsal and medial raphe are independently regulated, and the imbalance may contribute to depression severity and resistance. The reduced connectivity with right afferent fibers suggests dysregulation of the median raphe may originate upstream from the habenula.

Gosnell S, Curtis K, Velasquez K, Fowler J, et al: Habenular connectivity may predict treatment response in depressed psychiatric inpatients. *Journal of Affective Disorders* 2019;242:211–219. doi 10.1016/j.jad.2018.08.026. From Baylor College of Medicine; and the Michael E. DeBakey VA Medical Center, Houston, TX. **Funded by the McNair Medical Institute; and other sources. The authors did not include disclosure of potential conflicts of interest.**

Reference Guide

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

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 treatment efficacy.

Incidence Rate Ratio: The number of new cases of a condition in a defined (specified) group or population expressed as a ratio. For example, if there are 1000 people and a condition develops in 14 of them, the incidence rate is 14 per 1000 or 1.4%.

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

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

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).

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**
Founding Editor: **Michael J. Powers**

Statement of Editorial Policy: All of the information and opinions presented in each Psychiatry Alerts NOS article are strictly those contained in the cited article unless otherwise noted. Reader comments are welcome by mail, by telephone, or by email.

PSYCHIATRY ALERTS NOS

Cortisol and Depression/Anxiety Response	64
Light Therapy for Depression.....	64
Pharmacogenetic Test Approved	63
Pharmacogenetic Testing Panel.....	62
Reference Guide	66
Virtual Reality Exposure for Anxiety	65
VNS for Resistant Depression.....	61

Volume X / November 2018 / Number 11

www.alertpubs.com

Do you still need 2018 CME credits? It's not too late! See Back Page for Details.

Vagus Nerve Stimulation for Resistant Depression

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

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

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

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

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

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5641) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Individual issues are available for \$10.00 each. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

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

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

*See Reference Guide.

Minimum Panel for Pharmacogenetic Testing

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

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

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

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

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

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

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

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

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

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

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

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

Personal Pharmacogenetic Testing Approved

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

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

¹FDA News Release: FDA allows marketing of first direct-to-consumer tests that provide genetic risk information for certain conditions.

Available at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm>.

²FDA Drug Safety Communication: The FDA warns against the use of many genetic tests with unapproved claims to predict patient response to specific medications.

Available at <https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm624725.htm>.

Low-Level Light Therapy for Depression

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

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

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

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

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

Cortisol and Response to Psychological Therapies

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

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

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

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

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

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

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

Virtual Reality Exposure Therapy for Anxiety

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

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

Results: Compared with waitlist and psychological control conditions, VRET was more effective at reducing disorder-specific distress (effect size [ES],* 0.88), as well as behavioral (ES, 0.87), cognitive (ES, 1.15), and psychophysiological (ES, 0.64) outcomes, and general subjective distress (ES, 0.49). These results were maintained over various durations of follow-up.

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

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

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

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

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

*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.

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

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

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

Have you earned all the CME credit you need for 2018?

It's not too late to earn credit with your Psychiatry Alerts NOS subscription!

Visit www.alertpubs.com/continuing-education to learn how you can earn credit today.

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**
Founding Editor: **Michael J. Powers**

Statement of Editorial Policy: All of the information and opinions presented in each Psychiatry Alerts NOS article are strictly those contained in the cited article unless otherwise noted. Reader comments are welcome by mail, by telephone, or by email.

PSYCHIATRY ALERTS NOS

Adult ADHD: Diagnosis Consensus.....	71
Behavioral Addictions in Bipolar Disorder.....	69
CBT App for Opioid Use Disorder.....	69
Complementary Therapies in Pregnancy.....	70
E-Prescribing: Warning Accuracy.....	71
Functional Outcomes of High-Risk States.....	68
Neurocognitive Therapy in Schizophrenia.....	67
Reference Guide.....	72

Volume X / December 2018 / Number 12

www.alertpubs.com

Do you still need 2018 CME credits? It's not too late! See back page for details.

Integrated Neurocognitive Therapy in Schizophrenia

In patients with schizophrenia or schizoaffective disorder, integrated neurocognitive therapy (INT) appears to have beneficial effects on negative symptoms and functional outcomes, according to a meta-analysis of published trials.

Background: INT is designed specifically to address the 7 domains of cognition that may be impaired in patients with schizophrenia, according to the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) project: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition. Developed at the University of Bern, Switzerland, INT consists of 4 modules with specific interventions for each MATRICS domain.

Methods: The meta-analysis was based on a literature search for randomized controlled trials comparing INT with treatment as usual in adult patients with schizophrenia or schizoaffective disorder. The primary outcome measures were the Positive and Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF).

Results: The search identified only 2 studies, both from the group in Switzerland that pioneered INT. Participants in both studies received 30 biweekly 90-minute sessions of INT. The studies included a total of 217 participants, with a mean age of 35 years. The studies had high risk of bias because of nonblinding of patients and therapists, but risk of bias from other causes was generally low.

About 10% of patients dropped out of the studies during treatment, and another 13% dropped out during follow-up, which was conducted over 9–12 months. Compared with treatment as usual, INT was associated with a larger reduction in PANSS negative symptom scores after treatment (mean difference, 3 points; z score, * 4.12; $p < 0.0001$) and at follow-up (mean difference, 2.5 points; z score, 2.96; $p = 0.003$). Treatment had no significant effect on PANSS positive symptoms. Similarly, scores on the GAF improved to a significantly greater degree with INT than with treatment as usual post treatment (mean difference, 2.4 points; z score, 1.97; $p = 0.05$) and at follow-up (mean difference, 4.6 points; z score, 3.5; $p = 0.0004$).

PSYCHIATRY ALERTS NOT OTHERWISE SPECIFIED (ISSN 1559-5641) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Ave. Ste 111, Butler, NJ 07405. Telephone 973-898-1200. E-mail: psychnos@alertpubs.com. © 2018 by M.J. Powers & Co. Publishers. Written permission from M.J. Powers & Co. is required to reproduce material from this publication. Subscription \$105 a year in the U.S.; \$113.50 Canada; \$123.50 elsewhere; \$157.00 institutional. Subscribers may enroll in the 12-month CME program for \$83.00 per year. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

Discussion: While these results suggest that INT can improve negative symptoms and global functioning in patients with schizophrenia, the strength of the evidence is not strong because it is based on only 2 studies. Additional study of INT in schizophrenia appears to be warranted.

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

De Mare A, Cantarella M, Galeoto G: Effectiveness of integrated neurocognitive therapy on cognitive impairment and functional outcome for schizophrenia outpatients. *Schizophrenia Research and Treatment* 2018; doi 10.1155/2018/2360697. From Sapienza University of Rome, Italy. **Source of funding not stated. The authors declared no competing interests.**

*See Reference Guide.

Predicting Functional Outcomes of High-Risk States

A predictive machine learning model based on clinical data and MRI imaging was able to predict functional outcomes in patients at clinical high risk of psychosis (CHR) or with recent-onset depression (ROD). The model was generalizable across study populations from multiple European countries and also between these 2 high-risk populations.

Methods: The ongoing Personalized Prognostic Tools for Early Psychosis Management study is an attempt to develop prognostic signatures for poor functional outcomes in groups at risk for psychosis. The present study tested the geographic generalizability of models designed to predict 1-year functional outcomes in 116 individuals in the CHR state, 120 with ROD, and 176 age-, gender-, and site-matched controls. All participants had baseline MRI data available within the first 3 months of enrollment. Function was assessed at various time points using the Global Functioning: Social and Role scales. A poor outcome was defined as a score indicating mild but persistent or frequent impairment in either area of function. A machine learning program was used to develop 3 models that could predict functional outcomes: 1 based on baseline social and role functioning scores (e.g., current, lifetime highest, and highest and lowest in the past year); 1 based on gray matter volume images; and 1 combining both the clinical and neuro-imaging models. The models were compared with each other and with prognostic ratings by expert clinicians to determine which would best predict functional outcomes over 3–12 months.

Results: On average, patients were in their mid 20s at baseline. At follow-up, social and role impairment were present in about 55% of the CHR and ROD groups. In terms of predicting social impairment, accuracy was greatest with the combined clinical and neuroimaging model (63–65% for role functioning and 70–83% for social functioning) than with either of the individual models (accuracies of 55–68% and 65–77% for role and social functioning, respectively) and the predictions by expert clinicians (accuracy of 58–70%). Model accuracies were not affected in sequential comparisons each removing a single site's data, indicating that the models are geographically generalizable within the region. The clinical model outperformed the MRI-only-based model in overall accuracy and in transdiagnostic transferability. Clinician raters appeared to underestimate the risk of impairment in social and role functioning in both high-risk groups.

Discussion: These results suggest that use of a combined clinical and neuroimaging model could improve prognostic accuracy beyond current levels. However, given the high cost of MRI, combined prognostics may best be reserved for later in the process or for patients whose predicted clinical course is more ambiguous.

Koutsouleris N, Kambaitz-Illankovic L, Ruhrmann S, Rosen M, et al: Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite machine learning analysis. *JAMA Psychiatry* 2018;75 (November):1156–1172. From Ludwig-Maximilian-University, Munich, Germany; and other institutions. **Funded by the European Union; and other sources. Three of 25 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

CBT App for Opioid Use Disorder

The FDA has approved a mobile medical application intended to increase retention in outpatient treatment programs for individuals with opioid use disorder. The reSET-O program is prescription-based cognitive behavioral therapy (CBT) meant to be used in conjunction with outpatient treatment that includes buprenorphine (*Buprenex*) and contingency management. Contingency management is a behavior modification intervention that establishes a connection between new, targeted behaviors and the opportunity to obtain a desired reward. The app is not intended to be used as a stand-alone therapy, as a substitute for pharmacotherapy, or by patients whose primary language is not English.

A 12-week multisite trial evaluated adjunctive use of a desktop-based version of reSET-O (accessed at the clinic) in 170 patients receiving supervised buprenorphine treatment with a behavior therapy program and contingency management that rewarded negative urine tests. Although the use of reSET-O was not shown to decrease illicit drug use to a greater degree than buprenorphine and contingency management alone, patients who participated in the program did have a higher treatment retention rate than those who did not (82% vs 68%).

The FDA is focusing on making new tools and therapies available that can help those with opioid use disorder successfully treat their addiction. Because medical devices—including digital health products like the reSET-O app—may play an important role in these treatment efforts, the app received expedited approval.

FDA News Release: FDA clears mobile medical app to help those with opioid use disorder stay in recovery programs. Available at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628091.htm>.

Behavioral Addictions in Bipolar Disorder

Bipolar disorders are often comorbid with behavioral addictions, a category that includes compulsive gambling, kleptomania, internet addiction, and similar problems, according to a systematic literature review. Comorbid behavioral addiction predicts worse outcomes and more severe illness course than bipolar illness without behavioral addiction. There is currently no approved treatment for the combination, and the only treatment study had a negative result.

Bipolar disorder is associated with high impulsivity and an increased prevalence of substance use disorders. The concept of addiction has recently been broadened to include behavioral addictions, which are characterized by the repetitive occurrence of impulsive and uncontrolled acts, preceded by an urge or craving but without physiologic withdrawal symptoms. Comorbidity of behavioral addictions and bipolar disorder has not been thoroughly studied, and the directionality of the relationship is unclear.

A total of 28 observational studies on the co-occurrence of bipolar disorder and behavioral addictions were identified in the literature. Nearly all addressed specific behavioral addictions rather than the category; most of the studies (n=19) evaluated the prevalence of bipolar disorder in subjects with various behavioral addictions. The remaining 9 studies assessed behavioral addictions in patients with bipolar disorder. Rates of co-occurrence of bipolar disorder and behavioral addiction appear to be high. However, because the identified studies included small samples, overall estimates of comorbidity were not calculated.

Pathological gambling appears to be the most common behavioral addiction in bipolar disorder, followed by kleptomania, compulsive buying, compulsive sexual behavior, and internet addiction. Compared with patients who have bipolar disorder alone, those with co-occurring behavioral addiction have earlier age at onset; higher rates of comorbid Axis I conditions and

suicidal behavior; higher levels of impulsivity; a more severe course of illness; and a poorer prognosis. No treatments are currently approved specifically to treat the conditions together, and clinical management of these patients should first address affective instability and mood regulation, and then the behavioral addiction if still necessary. For these patients, psychological interventions that have been shown to prevent relapses and improve mood regulation in bipolar disorder (e.g., psychoeducation, family intervention, and cognitive behavioral, interpersonal, and social rhythm therapies) could be combined with step-based models, motivational interviewing, and cognitive behavioral therapies, which have had beneficial effects in addiction disorders.

Varo C, Murru A, Salagre E, Jiminez E, et al: Behavioral addictions in bipolar disorders: a systematic review. *European Neuropsychopharmacology* 2018; doi 10.1016/j.euroneuro.2018.10.012. From the University of Barcelona, Spain; and other institutions. **This study was conducted without specific funding. Two of 12 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Complementary Therapies in Pregnancy

Several complementary medicine approaches have the potential to reduce anxiety and depression during pregnancy and the postnatal period, according to a review. The evidence, although generally weak and limited, suggests acupuncture, bright light therapy, massage, and mindfulness training may be worth further investigation.

Background: The term complementary (in contrast to alternative) medicine refers to non-mainstream treatments that may be used in conjunction with conventional treatments. The most common types are mind–body practices and natural products.

Methods: A comprehensive literature search identified published controlled trials of complementary treatments in women who screened positive for or had a diagnosis of clinical anxiety or depression during the antenatal period. The primary outcome was antenatal anxiety or depression, as defined in each study.

Results: The search identified 20 trials with a total patient population of 1092 women. Interventions were mind–body practices (relaxation training, yoga, mindfulness, bright light therapy, massage, and acupuncture) and a natural product (omega-3 fatty acids). Control groups received a placebo or sham control, treatment as usual, information, time and attention, or a waiting list. Of the 20 trials, 15 examined depression and 8 examined anxiety. The overall study quality was low, with high rates of attrition, lack of blinding of participants or clinicians, and other issues.

Overall, mindfulness was not associated with significant reductions in depression severity, stress, or medication use in 3 trials. However, 1 of the studies did report a reduced rate of depression relapse (relative risk* [RR], 0.13). There was no evidence supporting an effect on antenatal anxiety. A small pilot study of acupuncture found no effect on rates of diagnosed depression or symptom severity, but a larger randomized trial found a significantly higher rate of recovery from depression (RR, 1.68) in treated women than in controls. Massage reduced antenatal depression symptom scores compared with the control (standard mean difference,* 0.73; $p > 0.001$), but did not reduce levels of anxiety. Bright light therapy was associated with a near-significant reduction in depression symptoms (standard mean difference from control, 0.75). No positive effects were found for yoga, relaxation, or omega-3 fatty acids.

Smith C, Shewamene Z, Galbally M, Schmied V, et al: The effect of complementary medicines and therapies on maternal anxiety and depression in pregnancy: a systematic review and meta-analysis. *Journal of Affective Disorders* 2019;245 (February 15):428-439. doi 10.1016/j.jad.2018.11.054. From Western Sydney University, Penrith, Australia. **This study received no specific funding. Three of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

Adult ADHD Diagnosis: European Consensus

The European Network Adult ADHD organization has updated its consensus statement on diagnosing and treating adult ADHD. The disorder is underdiagnosed in adults despite the availability of screening and diagnostic instruments.

Onset Timing. Most patients meet DSM-5 criteria for ADHD by the age of 12 years. However, clinicians should be aware that children with subthreshold symptoms at age 12 may go on to develop full ADHD criteria during adolescence. Whether late-onset ADHD exists is controversial, and many individuals in whom onset appears to be late likely met full criteria at some time during childhood.

Screening. Valid screening tools exist, but it is important to know whom to screen for ADHD in adulthood. The consensus statement recommends that screening be offered to anyone who has a chronic history of inattentive, restless, or impulsive behaviors, as well as individuals with emotional instability. Target groups include family members of a person with ADHD, persons with a history of behavioral problems, those with any chronic mental health disorder, those with multiple physical diseases, and persons involved with the criminal justice system. Two widely accepted screening tools are freely available: The Adult ADHD Self-Report Scale and the Wender Utah Rating Scale, which assesses other symptoms that may accompany ADHD, in addition to the core symptoms.

Diagnosis. Use of a semistructured interview is recommended, and clinicians should take care to fully assess impairment, psychiatric history, and substance use. The Diagnostic Interview for ADHD in adults, second edition (DIVA-2), is based on the DSM-IV-TR criteria and is available online and as an app. DIVA-2 is currently being updated to conform to DSM-5 criteria. The ACE+, which assesses ADHD core symptoms, impairment, and co-existing conditions, is also available online. Alternatives that are not open-access are the Conners Adult ADHD Diagnostic Interview for DSM-IV and the Adult ADHD Clinical Diagnostic Scale. Diagnosis of ADHD in adults is based on a lifetime history of symptoms and impairment. Assessment of childhood and current symptoms is essential, and symptoms and impairment must be present in 2 domains: school, work, home, or interpersonal contacts. Collateral information from family members and the spouse may be useful. Persons with ADHD have particularly high rates of comorbidity for mood, anxiety, eating, sleep, substance use, and behavioral disorders. Comorbidity should be fully investigated before any treatment begins. See the current issue of *Psychiatry Drug Alerts* for the organization's recommendations regarding treatment of Adult ADHD.

Kooij J, Bijlenga D, Salerno L, Jaeschke R, et al: Updated European consensus statement on diagnosis and treatment of adult ADHD. *European Psychiatry* 2019;56:14–34. doi 10.1016/j.eurpsy.2018.11.001. From the Expertise Center Adult ADHD, the Netherlands; and other institutions. **The consensus statement was created with no external funding. Of 64 study authors, 19 disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Accuracy of E-Prescribing Warnings

Use of electronic prescribing systems is common and even mandated in some states and/or institutions. These programs use computerized decision algorithms to automate warnings about potential prescribing errors. However, according to a survey of practicing psychiatrists, inaccurate warnings commonly appear.

The American Society of Clinical Psychopharmacology distributed an email survey to >1200 members regarding their experiences with e-prescribing. About 10% of members responded to the survey, 78% of whom used an e-prescribing system. The majority of electronic prescribers

(83%) reported that the system delivered automated warnings about potentially problematic prescriptions, and one-third of these respondents believed their system produced incorrect warnings. Of those who believed inaccurate warnings were produced, one-third believed $\geq 50\%$ of the warnings were inaccurate. Prescribers reported that erroneous warnings included dosing ranges (54% of respondents), drug interactions (50%), contraindications (42%), dosing frequency (38%), dosing time (13%), drug indications (13%), and "other" (9%). Nearly all prescribers who believed some warnings to be incorrect (96%) reported their system allowed them to override a warning they believed was inaccurate or to describe their rationale for the prescription. However, few were able to report the inaccuracy within the system. Almost universally, prescribers reported that overriding the inaccurate warnings was slightly or moderately burdensome to their practice.

Although based on a small number of responses, these survey results suggest that incorrect prescribing alerts for psychotropic medications are common and burdensome. Despite their problems, electronic prescribing alerts have been shown to reduce the incidence of medication errors and adverse effects. However, "alert fatigue," due to the number of warnings may desensitize prescribers to the notifications and lead them to ignore or override appropriate warnings.

Phillips K, Citrome L: Inaccurate prescribing warnings in electronic medical record systems: results from an American Society of Clinical Psychopharmacology membership survey. *Journal of Clinical Psychiatry* 2019 doi 10.4088/JCP.18ac12536. From New York-Presbyterian Hospital, NY; and other institutions. **The survey was conducted and reported with no external funding. Both study authors disclosed potentially relevant financial relationships.**

Reference Guide

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.

Standardized Mean Difference: The difference between two normalized means - i.e. the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales, a value of 0 to 0.2 is considered a negligible effect, 0.2 to 0.5 a small effect, 0.5 to 0.8 a medium effect, and >0.8 a large effect.

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).

Z Score: A statistical measurement of a score's relationship to the mean in a group of scores. A Z-score of 0 means the score is the same as the mean.

Have you earned all the CME credit you need for 2018?

It's not too late to earn credit with your Psychiatry Alerts NOS subscription!

Visit www.alertpubs.com/continuing-education to learn how you can earn credit today.

Executive Editor: **Trish Elliott** Associate Editor: **Tara Hausmann**
Contributing Editors: **Kate Casano, MSHyg, Bennett Silver, MD**
Assistant Editor: **Donna Foehner** Consulting Editor: **John C. Rose, MD**
Founding Editor: **Michael J. Powers**

Statement of Editorial Policy: All of the information and opinions presented in each *Psychiatry Alerts NOS* article are strictly those contained in the cited article unless otherwise noted. Reader comments are welcome by mail, by telephone, or by email.