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ECT Augmentation for Resistant Schizophrenia

In a randomized trial, augmentation with ECT was effective, safe, and well tolerated in patients with clozapine-resistant schizophrenia.

Methods: Study participants were adults with schizophrenia that had been resistant to ≥2 antipsychotic trials at adequate doses for 4 weeks each plus 12 weeks of clozapine treatment dosed to reach a blood level of ≥350 ng/mL. Patients were required to have at least moderate psychotic symptoms despite current clozapine treatment. Participants were randomly assigned to continue their background clozapine dose for 8 weeks or to receive add-on ECT, which was administered bilaterally 3 times a week for 4 weeks and then twice weekly for 4 weeks. Those who completed the clozapine-only arm of the study were offered adjunctive ECT at study end. Response was defined as an improvement of ≥40% on the Brief Psychiatric Rating Scale (BPRS) psychotic symptom subscale, a Clinical Global Impression (CGI)–Severity rating of mild or less, and a CGI–Improvement rating of much improved. The BPRS improvement threshold was placed higher than the usual cutoff of 20% to balance the greater burden and complexity of ECT. Patients were evaluated clinically by blinded raters.

Results: A total of 39 patients received randomized treatment: 20 with ECT and 19 with continued clozapine. Of these, 3 in the clozapine group and 2 in the ECT group dropped out early and refused further treatments but were included in the efficacy analysis, as was 1 patient who discontinued ECT because of persistent involuntary movements.

At the 8-week evaluation, 10 of 20 patients in the ECT-augmentation group (50%) met response criteria, compared with none of patients in the clozapine-only group. Using a lower threshold of a ≥20% improvement, there were 12 responders to augmentation (60%) and still none with clozapine. Patients in the ECT group had significantly lower psychotic symptom scores beginning in the third study week and lasting throughout the trial. All patients in the clozapine-only group went on to receive add-on ECT at the end of the 8-week study period. At the end of the crossover phase, 9 of these 19 patients (47%) met response criteria. Overall, the response rate was 49%. ECT had no effect on negative symptoms.

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Mild, transient confusion after ECT was reported by 2 patients. There were no other adverse effects in the ECT group. Neurocognitive testing showed reduced speed of processing, consistent with the known clinical experience with ECT.

Discussion: Reportedly 45–70% of patients who receive clozapine do not experience major improvement. Pharmacological augmentation of clozapine can include additional antipsychotics, mood stabilizers, anxiolytics, antidepressants, and glutamatergic agents. However, none of these strategies have irrefutable evidence to support their efficacy. The response rates in the present study appear to be the highest reported for any type of clozapine augmentation, but further study is needed to determine the durability of response and the need for maintenance treatment.

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

Petrides G, Malur C, Braga R, Bailine S, et al: Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *American Journal of Psychiatry* 2015;172 (January):52–58. From the Zucker Hillside Hospital, Glen Oaks; and the Feinstein Institute for Medical Research, Manhasset, NY. **Funded by the NIMH. Four study authors disclosed financial relationships with commercial sources; the remaining 7 authors declared no conflicts of interest.**

***See Reference Guide.**

Psychological Therapies for Menopausal Depression

Although depression is very common during the menopausal transition, a review of the published literature indicates that data on the efficacy of psychological treatments are generally positive but extremely limited.

Methods: The authors of this review initially searched for clinical trials of cognitive behavioral, behavioral, and mindfulness-based (CBBMB) therapies for menopausal depression. Finding only 2, they expanded the search to include studies of the effects of CBBMB therapies on "depression symptoms" as an outcome of analyses mainly designed to address hot flashes or menopausal symptoms.

Results: A total of 14 studies were identified. Only 2 examined specific treatment of menopausal depression, both using cognitive behavioral therapy (CBT). Both studies showed positive results. In the first study of 169 peri- or postmenopausal women, half of patients had a ≥50% reduction in symptom scores on the Hamilton Rating Scale for Depression and just over 25% experienced complete remission. The second, smaller study (n=44) found a statistically ($p=0.01$ vs. control) and clinically significant benefit of CBT, with symptom severity ratings decreasing from severe to minimal.

Of the 14 studies, 5 addressed the effects of CBBMB therapies on menopausal symptoms and 7 evaluated their effects on hot flashes; all 12 included depressive symptoms as a secondary outcome. Only 2 of the studies, both with a primary outcome of hot flashes, examined mindfulness-based therapies. Several of these studies found cognitive-based group treatments effective at reducing depressive symptoms. Effects of the treatments on depressive symptoms in women experiencing hot flashes were mixed or transient.

Discussion: Psychological treatments are a needed option for menopausal women, many of whom should not or prefer not to take antidepressants or hormonal treatments. While the results of the trials of manualized, standard CBT for menopausal depression were promising, large, randomized, controlled trials of CBT-based programs specific to menopause are lacking at this time.

Green S, Key B, McCabe R: Cognitive-behavioral, behavioral, and mindfulness-based therapies for menopausal depression: a review. *Maturitas* 2014; doi 10.1016/j.maturitas.2014.10.004. From McMaster University; and St. Joseph Healthcare, Canada. **This review was conducted without funding. The authors declared no conflicts of interest.**

ECT vs. Medication for Resistant Bipolar Depression

In a randomized multicenter trial, ECT was superior to algorithm-based medication in acute treatment of resistant bipolar depression.[1]

Methods: Study participants were inpatients with a diagnosis of type I or II bipolar disorder who were experiencing a depressive episode. Study patients were required to have a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥25 and to have had a lack of response to ≥2 adequate trials of lithium, lamotrigine, quetiapine, or olanzapine. Participants were randomly assigned to receive either the antidepressant drug treatment for 6 weeks according to a published algorithm (see table), or standardized ECT 3 times a week for up to 6 weeks. Those assigned to ECT who achieved remission in <6 weeks were switched to the antidepressant therapy. The primary outcome measure was the MADRS, assessed by blinded raters, with response defined as a ≥50% reduction in score and remission as a score of ≤12.

Results: A total of 66 patients were enrolled, received ≥1 post-baseline assessment, and were included in the intent-to-treat analysis.* Four patients in the ECT group achieved euthymia or remission before completing the study and were lost to follow-up. Discontinuation rates in the 2 groups did not differ statistically. Patients in the ECT group completed a mean of 11 treatments. Of those in the medication group, only 1 received monotherapy.

Medication Treatment Algorithm[2]	
Patients Not Receiving a Mood Stabilizer	**Patients Receiving Lithium or Valproate**
1. Start lamotrigine plus lithium or valproate. For severe depression, consider an antidepressant plus an antimanic mood stabilizer. For psychotic depression, add an atypical antipsychotic.	1. Increase lithium dosage to serum concentration between 0.8 and 1.2 mEq/L. Add lamotrigine.
2. Add quetiapine.	
3. Consider replacing quetiapine with olanzapine–fluoxetine combination.	
4. Discontinue olanzapine–fluoxetine combination, add an antidepressant, and maximize antimanic mood stabilizer.	

MADRS scores decreased in both groups from baseline means of 38 and 39 points in the medication and ECT groups, respectively; at week 6, the change was 7 points greater with ECT than medication (p=0.002). In addition, MADRS scores changed at a more rapid rate in the ECT group (p=0.03). Secondary outcomes—the Inventory of Depressive Symptomatology and the Clinical Global Impression–Bipolar Version scale—also significantly favored ECT. Among patients who completed 6 weeks of treatment, 17 patients in the ECT group experienced response, as did 7 in the medication group (74% vs. 35%; p=0.01). Remission occurred in 8 patients who completed the ECT protocol, compared with 6 patients in the medication group, a non-significant difference.

Discussion: Most current guidelines recommend ECT as second-line treatment for resistant bipolar depression. These results suggest that ECT may be more effective than medication. However, there is a need to develop treatments with better remission rates.

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

[1]Schoeyen H, Kessler U, Andreassen O, Auestad B, et al: Treatment-resistant bipolar depression: a randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. *American Journal of Psychiatry* 2015;172 (January):41–51. From Stavanger University Hospital, Norway; and other institutions. **Funded by the Western Norway Regional Health Authority. Four study authors disclosed financial relationships with commercial sources; the remaining 5 authors declared no conflicts of interest.**

[2]Kessler U, et al: The study protocol of the Norwegian randomized controlled trial of electroconvulsive therapy in treatment resistant depression in bipolar disorder. *BMC Psychiatry* 2010; 10:16.

Drug Trade Names*: lamotrigine—*Lamictal*; olanzapine—*Zyprexa*; olanzapine–fluoxetine—*Symbyax*; quetiapine—*Seroquel*; valproate—*Depakene, Depakote

***See Reference Guide.**

Non-Drug Treatments for Agitation in Dementia

Agitation in dementia has been regarded as the product of brain changes and is often treated with medication. However, commonly used psychotropics are discouraged because they are believed to be ineffective and can have serious adverse effects. Results of a systematic review now suggest that agitation in dementia may arise from an unmet need that the patient is unable to communicate. The review found the most effective interventions are those that train clinicians to understand agitation as a symptom of unmet need, such as physical discomfort or a desire for stimulation, emotional comfort, or communication.

Methods: The investigators searched multiple databases for studies that evaluated nonpharmacological interventions for agitation in patients with dementia. Agitation was measured quantitatively, and the studies had to include a comparison group. The analysis was limited to randomized controlled trials of high methodologic quality and with >45 participants. Studies included interventions to prevent as well as treat agitation.

Results: A total of 33 studies were included in the analysis. The most effective interventions involved working through the care-home staff, encouraging caregivers to treat patients as individuals rather than being task-focused. Studies of person-centered care training, communications-skills training, and care mapping found these interventions to be effective both during the intervention and after months of follow-up. These interventions were associated with a 30% decrease in measured agitation.

Sensory interventions targeted people in care homes, providing touch stimuli (e.g., massage) or multisensory stimulation. Touch was found to have a positive effect, but only during the stimulation. Similarly, music therapy and group activities were effective during the intervention, but there was no evidence of long-term efficacy.

Light therapy, aromatherapy, and training family members in cognitive behavioral therapy or behavior management therapy were not found to be effective. The authors suggest that training family members in these complex therapeutic routines and skills may be almost impossible to combine with caring for their relative. Evidence was insufficient to establish or rule out the efficacy of exercise, training caregivers without supervision, or simulated presence therapy.

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

Livingston G, Kelly L, Lewis-Holmes E, Baio G, et al: Non-pharmacological interventions for agitation in dementia: systematic review of randomised controlled trials. *British Journal of Psychiatry* 2014;205 (December):436–442. From University College London, U.K. **Funded by the UK National Institute for Health Research. The authors declared no conflicts of interest.**

***See Reference Guide.**

CBT Protocol for Anxiety in Dementia

A growing evidence base supports the belief that people with dementia can learn and develop skills, even if moderately cognitively impaired. Anxiety is a common problem in patients with dementia and is often treated with psychoactive medication. However, due to safety concerns and limited efficacy, alternative nonpharmacological treatments are needed. In an effort to fulfill this need, a 10-session cognitive behavioral therapy (CBT) approach has been developed to treat anxiety in patients with mild-to-moderate dementia. The program was used effectively in a clinical trial in 50 patients, with results pending publication. (See Editor's Note below.)

The therapy is divided in 3 phases covered in weekly sessions. As with other forms of CBT, Phase 1 (4 sessions) focuses on introductions; rapport building; socialization to the cognitive

model; addressing barriers to participation; and setting goals. Phase 2, the intervention phase, addresses 4 key goals, each with its own module: autonomic reactions (both physiologic and behavioral); strategic reactions; rules for living (both habitual and new); and interpersonal aspects of dementia, such as sharing others' concerns and points of view. Phase 3 consists of the usual CBT focus on consolidation: maintaining gains and integrating skills into daily life.

The therapeutic program is based on a generic cognitive model of anxiety that is applicable to all forms. It includes the concept of "cognitive specificity," in which anxiety is characterized by a sense of the self as vulnerable to environmental chaos and uncertainty, and aims to reduce anxiety by finding alternatives to self-defeating behaviors and increasing appraisals of safety and personal efficacy. The therapy is described as person-centered because it is highly flexible, using individual tailoring to compensate for cognitive deficits. The program covers specific content areas and goals, but these can be selectively shortened or omitted to keep the program within the capabilities of the client. It also enlists the help of a family member or friend to serve as a "supportive other" when available.

Treatment is based on core CBT aspects including session structure, socialization to the cognitive model, understanding a cognitive model of anxiety, self-monitoring, and other elements. It differs from standard CBT in offering more flexibility with regard to pace, use of the client's own words and formulations, goal-setting in the middle phase of therapy, and the use of a supportive other. Strategies to work with neurocognitive impairment are a vital part of the program and differ in their details according to the individual's cognitive profile and to specific deficits associated with each of the major types of dementia. These strategies include taking advantage of the "scaffolding" of CBT, with session structure and strategies for retention of new learning; cognitive rehabilitation; and supportive learning of pre-therapy skills such as a vocabulary of emotions and the ability to monitor emotional states. The supportive other provides memory prompts, which help the client generalize work from therapy into everyday life.

Editor's Note: *Psychiatry Alerts NOS* will cover the results of this study when they have been published.

Charlesworth G, Sadek S, Schepers A, Spector A: Cognitive behavior therapy for anxiety in people with dementia: a clinician guideline for a person-centered approach. *Behavior Modification* 2014; doi 10.1177/0145445514561317. From University College London, U.K.; and other institutions. **Funded by the U.K. National Institute for Health Research. The authors declared no conflicts of interest.**

Hair Follicles as a Source of Psychiatric Biomarkers

Scalp hair follicles may be a promising source of surrogate genetic markers for mental illnesses, according to a study that identified candidate RNA markers for schizophrenia and autism.

Background: Brain and hair follicles are both ectodermic tissues, sharing the same developmental origin. Difficulty obtaining brain tissue has hampered the search for novel biomarkers that would lead to new diagnostic tools and individualized treatments.

Methods: Schizophrenia-relevant genes—those related to the GABAergic system, myelin, and fatty acids—were explored in patients and controls. Messenger RNA (mRNA) analyses were carried out on 10 hairs plucked from the scalp of each study participant. The schizophrenia study included an exploratory sample set of 52 patients and 62 local control subjects. Results were validated in a second set of 42 patients and 55 controls and in postmortem brains of patients with and without schizophrenia. A final analysis compared candidate genes in the hair follicles of 18 patients with autism and 24 controls.

Results: Of 22 genes evaluated in the exploratory schizophrenia patient set, 7 were differentially expressed in patients and controls. When evaluated in the confirmatory set, only 1 gene, the fatty acid-binding protein FABP4, showed significantly reduced expression (40–43%) in patients with schizophrenia. Expression of this gene was not related to patient age; gender; dose of antipsychotic medication; duration of illness; metabolic status; or recent nutritional status. The authors concluded that FABP4 was a robust marker for schizophrenia, with a sensitivity* of 72% and specificity* of 67% to distinguish patients from healthy controls. In postmortem brain samples, FABP4 transcript expression was significantly elevated in the frontal cortex in those with schizophrenia, compared with controls.

The autism study was a preliminary investigation of 9 candidate genes. The set included FABP4 because of the genetic overlap between schizophrenia and autism. However, only 1 gene, CNTNAP2, appeared to be a valid marker for autism. These results need to be replicated in confirmatory analyses.

Discussion: The authors suggest that the abnormal expression of FABP4 in hair follicles may point toward a pathophysiological step in schizophrenia. Clinically, FABP4 expression levels may prove to be a useful and easily collectible marker to identify prodromal schizophrenia in individuals who appear to be at risk.

Maekawa M, Yamada K, Toyoshima M, Ohnishi T, et al: Utility of scalp hair follicles as a novel source of biomarker genes for psychiatric illnesses. *Biological Psychiatry* 2014; doi 10.1016/j.biopsych.2014.07.025. From RIKEN Brain Science Institute, Saitama, Japan; and other institutions. **Funded by the Japan Society for the Promotion of Science; and other sources. The authors declared no conflicts of interest.**

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Intent-to-Treat (ITT) Analysis: 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.

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

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

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Group CBT for Hypochondriasis

Combined individual and group cognitive behavioral therapy resulted in large improvements in hypochondriasis symptoms in an uncontrolled study. The treatment was well accepted, and improvements persisted for 12 months. Group sessions can be considered an effective and economical way to extend the coverage of CBT for hypochondriasis.

Methods: The study, conducted at a university outpatient psychotherapy unit in Germany, enrolled participants with a primary DSM-IV diagnosis of hypochondriasis and who were free of major medical illness or suicidal ideation. All patients received 6 individual CBT sessions interspersed with 8 group sessions, followed by an individual booster session. The group sessions lasted 100 minutes and were mainly informational, avoiding unstructured discussion of patients' health concerns. The 50-minute individual sessions addressed patients' individual dysfunctional fears and beliefs and included some exposure to illness imagery and in-vivo exposure, such as a hospital visit. The study used 3 primary efficacy measurements: beliefs and attitudes about illness and hypochondriasis (Illness Attitudes Scales [IAS]), beliefs relevant for the maintenance of health anxiety (the Cognitions About Body and Health Questionnaire [CABAH]), and dysfunctional illness behavior (Scale for the Assessment of Illness Behavior [SAIB]).

Results: A total of 80 patients participated in the study. In addition to hypochondriasis, they had a mean of 2 comorbid disorders, most often affective or anxiety disorders. A total of 13 patients dropped out of therapy, most because of lack of motivation.

Patients showed statistically significant improvement from baseline to treatment completion on the 3 primary study outcome measures ($p<0.001$ for all 3 in both the completer and intent-to-treat analyses*), with effect sizes* of 1.08 for the IAS, 0.84 for the CABAH, and 0.82 for the SAIB. These improvements persisted and even increased by the 12-month follow-up. Secondary study outcome measures of somatic symptoms and general psychopathology also showed statistically significant improvement, with small-to-medium effect sizes (0.46–0.72) at 12

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months. Patients were satisfied with the treatment overall and generally felt that discussions of alternate reasons for physical symptoms were the most helpful component of CBT.

After the study, 59 patients (74%) continued individual CBT, receiving a mean of 18 additional treatments. Outcomes for these patients did not differ from those for patients who received no additional therapy. Patients with the most severe baseline symptom scores experienced the greatest improvement with treatment.

Weck F, Gropalis M, Hiller W, Bleichhardt G: Effectiveness of cognitive-behavioral group therapy for patients with hypochondriasis (health anxiety). *Journal of Anxiety Disorders* 2015;30 (March):1–7. From Johannes Gutenberg University of Mainz; and Philipps University Marburg, Germany. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

Transcranial Stimulation for Auditory Hallucinations

In a randomized crossover trial, repetitive transcranial magnetic stimulation (rTMS) was not superior to sham treatment in reducing auditory hallucinations.[1]

Background: Various rTMS paradigms have been investigated for treating auditory hallucinations. According to a recent meta-analysis,[2] low-frequency rTMS to the left temporoparietal area has a moderate effect size* of about 0.5. The efficacy of bilateral versus unilateral stimulation, the effect of stimulation to different brain areas, and whether certain types of patients are more responsive remain undetermined. Broca's area is involved in language production and is suspected to contribute to the inner-speech model of auditory hallucinations. The present study was the first to target Broca's area with high-frequency stimulation but without a unilateral rTMS treatment condition.

Methods: In the study, 23 adults, aged 18–50 years, with schizophrenia spectrum disorders and auditory hallucinations persisting for >6 months despite adequate trials of ≥2 antipsychotic drugs, received both active and sham rTMS in random order. Active treatments were all bilateral and included low-frequency (1 Hz) rTMS to the temporoparietal area, high-frequency (20 Hz) temporoparietal rTMS, and high-frequency rTMS to Broca's area. Sham treatment used active rTMS coils with the front edge touching the scalp at a 45-degree angle.

Results: Positive and general symptoms of schizophrenia, but not negative symptoms, showed significant improvement following treatment. Auditory-hallucination severity also decreased by a small but statistically significant amount over time in all treatment groups, including sham rTMS. There was no difference in response across the active and sham treatment groups, and response did not differ based on stimulation frequency or target area.

[1]Kim E-J, Yeo S, Hwang I, Park J-I, et al: Bilateral repetitive transcranial magnetic stimulation for auditory hallucinations in patients with schizophrenia: a randomized controlled, cross-over study. *Clinical Psychopharmacology and Neuroscience* 2014;12 (December):222–228. From Chonbuk National University, Jeanju, Korea; and other institutions. **Funded by the Kim Jae Jung Memorial Fund; and other sources. The authors did not include disclosure of potential conflicts of interest.**

[2]Slotema C, et al: Review of the efficacy of transcranial magnetic stimulation for auditory verbal hallucinations. *Biological Psychiatry* 2014;76 (July):101–110.

***See Reference Guide.**

Continuation DBS

In a randomized crossover trial, withdrawal of deep brain stimulation to the cingulate gyrus was associated with worsening in patients with severe refractory depression who had previously experienced response to the treatment. Although some patients may experience benefits of DBS for a time after active stimulation is discontinued, these results suggest that antidepressant response is lost unless stimulation is continued.

Background: DBS has been successfully used in patients with severe, refractory depression, but study sample sizes have been too small to bring about much clinical guidance. Previous studies, generally open-label and uncontrolled, support the efficacy of stimulation to the subcallosal cingulate gyrus, nucleus accumbens, and the ventral capsule/ventral striatum. The optimal site and duration of treatment remain areas of active research.

Methods: Study participants were adults with severe depression, refractory to multiple treatments including medication, psychotherapy, and/or ECT. Of 8 patients who had electrodes implanted and received DBS to the cingulate gyrus, 5 achieved stable clinical remission (i.e., 17-item Hamilton Rating Scale for Depression [HAM-D] score <8) and were enrolled in the withdrawal trial. The 5 patients were then randomly assigned to 3 months of continued stimulation followed by sham stimulation for 3 months (ON-OFF) or the reverse (OFF-ON). Clinical assessments were performed every 2 weeks by a psychiatrist who was blinded to treatment assignment. Relapse was defined as a HAM-D score >14. Patients with 2 assessment visits in a relapsed state were withdrawn from randomized treatment.

Results: During active stimulation, 4 of the 5 patients maintained their clinical remission, compared with 2 patients during sham stimulation. During sham treatment, 2 patients experienced a relapse, and 1 worsened but did not meet relapse criteria. One patient was withdrawn from the trial during the OFF phase because of a serious relapse. Another patient, who experienced a relapse during the initial OFF phase, was switched to ON treatment and recovered. No patient required a change in medication. Average HAM-D scores were higher during OFF than ON treatment (p=0.025).

Discussion: Possible explanations for the efficacy of DBS include the effects of electrode stimulation, nonspecific local changes due to electrode implantation, and an unlikely placebo effect. The present study supports a direct effect of DBS. Patients were clinically stable for an average of 6 months before the study, and there were no changes to their medication regimen, suggesting that relapses were truly a consequence of turning off the stimulation.

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

Puigdemont D, Portella M, Perez-Egea R, Molet J, et al: A randomized double-blind crossover trial of deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: a pilot study of relapse prevention. *Journal of Psychiatry & Neuroscience* 2015; doi 10.1503/jpn.130295. From the Autonomous University of Barcelona, Spain; and other institutions. **Funded by the Fondo de Investigacion Sanitaria; and other sources. Three study authors disclosed financial relationships with commercial sources; the remaining 8 authors declared no conflicts of interest.**

***See Reference Guide.**

Schema Therapy for Mixed Personality Disorders

Group schema therapy was feasible and showed preliminary evidence of efficacy in a pilot study in a mixed diagnostic group of patients with personality disorders and Axis I comorbidity.[1] These results suggest that the group process may have special value in challenging maladaptive schemas.

Background: Schema therapy, one of a "third wave" of treatments developed specifically for treating personality disorders and other complex, chronic problems, has demonstrated efficacy in borderline personality disorder. The present study was conducted to lay the groundwork for a larger randomized controlled trial of group schema therapy in patients with different personality disorders.

Methods: Study subjects were 8 adults with borderline personality disorder (n=2), avoidant personality disorder (n=5), and avoidant personality disorder with comorbid schizoid and dependent personality disorders (n=1). All patients also had comorbid major depression, and

7 had clinically significant anxiety. Treatment consisted of 20 weekly, 60-minute sessions of therapy, adapted from a published protocol of group schema cognitive behavioral therapy,[2] with an emphasis on schema mode work and experiential change techniques. Participants were encouraged to connect with each other to create a safe group climate. After education about the approach, patients rated the severity of their top 3 maladaptive schemas and modes each week and worked on behavioral change to challenge these modes. Outcomes were measured with the Millon Clinical Multiaxial Inventory (MCMI-III) for DSM-IV diagnoses, the Young Schema Questionnaire: Short form, second version (YSQ-S2), the Schema Mode Inventory (SMI), and the Symptom Checklist-90-Revised (SCL-90-R).

Results: The 2 patients with borderline personality disorder dropped out of treatment after 3 and 16 sessions, respectively, citing shame and distress about returning after missing sessions. The remaining 6 participants completed treatment and were included in the outcome analysis. At the end of treatment, 4 of these patients no longer met diagnostic criteria for their personality disorder based on the MCMI-III, responses that persisted after 6 months of follow-up. A fifth group member no longer met diagnostic criteria after 6 months. No patient continued to meet criteria for depression by the end of treatment, and mood continued to improve from post-treatment to 6 months. For 3 patients, anxiety symptoms were no longer in the clinical range. Scores for several of the maladaptive schema decreased significantly. Effect sizes* for all of the outcome variables were in the large range, both short- and long-term. (See table.)

Treatment Effect Sizes

	YSQ-S2	Avoidant	Anxiety	Depression	Global Symptoms	SMI Adaptive	SMI Maladaptive
Pre- to post-treatment	2.2	2.96	0.76	2.91	1.06	1.32	1.69
Pre-treatment to follow-up	2.7	3.07	0.82	2.44	1.14	1.22	1.66

At the end of treatment, patients participated in a focus group, which was recorded and analyzed for themes. In this session, patients reported that therapy in a group setting normalized their schemas and associated emotional experiences, gave them practice in challenging their schemas, removed inhibitions on self-expression, and motivated them to make behavioral changes.

[1]Skewes S, Samson R, Simpson S, van Vreeswijk M: Short-term group schema therapy for mixed personality disorders: a pilot study. *Frontiers in Psychology* 2015; doi 10.3389/fpsyg.2014.01592. From the University of South Australia, Adelaide; and G-kracht Psychomedisch Centrum BV, Delft, Netherlands. **Source of funding not stated. The authors declared no conflicts of interest.**

[2]van Vreeswijk M, Broersen, J. (2013). *Short-term group therapy scheme; cognitive behavioral therapy techniques*. Houten, Netherlands: Bohn Stafleu van Loghum; 2013.

***See Reference Guide.**

Amino Acid Profiling in Major Depression

Plasma amino acid profiling identified differences between subjects with major depressive disorder and healthy controls. Profiles also differed in patients whose symptoms did and did not respond to SSRI therapy. These results support previous evidence that disarrangement of metabolic function may contribute to the development of depression.

Methods: Amino acid profiling was carried out in 68 patients with a DSM-IV diagnosis of major depressive disorder at baseline, and then again 6 weeks after the start of SSRI therapy. In addition, 22 healthy controls with no family history of depression were included. A total of 40

different amino acids were assayed in plasma using liquid chromatography-tandem mass spectrometry. The primary clinical endpoint for SSRI therapy was response (i.e., ≥50% reduction in Hamilton Rating Scale for Depression score) by week 6.

Results: At baseline, 10 amino acids showed different expression between patients with and without depression. A total of 48 patients (71%) experienced response to SSRI therapy. Compared with nonresponders, those who responded had higher expression of α-aminobutyric acid (ABA) at baseline. The average ABA concentration was reduced after treatment in the response group, but not in the nonresponse group. The relationship of therapeutic response to the change in ABA persisted after adjustment for baseline clinical variables, which suggests ABA is not merely a marker for depression severity. Changes in several other amino acids, as well as the ratio of tryptophan to large neutral amino acid, were also correlated with response.

Discussion: These findings suggest disarrangement and restoration of systemic metabolic status may be involved in the development and improvement of depression. ABA is a general marker of various conditions including malnutrition, sepsis, and liver disease. In patients with depression, high levels of ABA may reflect metabolic disturbance secondary to poor appetite or an underlying hypometabolic state that may arise from mitochondrial dysfunction, a proposed mechanism of major depression. Disturbances in the amino acid profile may also reflect glutamatergic abnormalities.

Woo H-I, Chun M-R, Yang J-S, Lim S-W, et al: Plasma amino acid profiling in major depressive disorder treated with selective serotonin reuptake inhibitors. *CNS Neuroscience & Therapeutics* 2015; doi 10.1111/cns.12372. From Sungkyunkwan University School of Medicine, Korea; and other institutions. **Funded by the Korean Ministry of Health and Welfare. The authors declared no conflicts of interest.**

Treatment of Insomnia in Bipolar Disorder

Results of a pilot study of insomnia-specific cognitive behavioral therapy (CBT) suggest that sleep disturbance may be an important modifiable mechanism of bipolar disorder.

Methods: For the present study, a bipolar disorder-specific modification of CBT for insomnia (CBTI-BP) was developed and integrated elements of interpersonal and social rhythm therapy, chronotherapy, and motivational interviewing. The 58 study participants were patients with bipolar I disorder who were interepisode and met the International Classification of Sleep Disorders diagnostic criteria for general insomnia disorder. Patients were randomly assigned to receive 8 sessions of either CBTI-BP or psychoeducation. CBTI-BP was flexibly designed for each patient and included a varying "dose" of behavioral elements related to sleep hygiene, cognitive strategies to reduce anxiety and alter unhelpful beliefs about sleep, and a module to improve daytime functioning by introducing energy-generating physical activities. The primary outcome of the study was mood-disorder relapse.

Results: A total of 3 patients in each group dropped out of the study before receiving any treatment, a further 3 in each group dropped out during the intervention, and 5 more were unavailable for 6-month follow-up. During treatment, relapse rates and days spent in bipolar episodes did not differ between the 2 treatments. During 6 months of follow-up, relapse was significantly less frequent in patients who received CBTI-BP, who also spent markedly less time in a bipolar episode. (See table). Although both groups experienced improvement in insomnia symptoms, the effects were larger in the CBTI-BP group. The CBTI-BP group also had higher rates of response and remission, both immediately post-treatment and at 6 months, as measured on 2 separate scales, the Insomnia Severity Index and the Duke Structured Interview for Sleep Disorders. There were no between-group differences in improvement in functional impairment. Patients who received CBTI-BP had a somewhat higher rate of discontinuation of sleep medication than the psychoeducation group.

Mood and sleep outcomes during follow-up				
	CBTI-BP (n=30)	Psychoeducation (n=28)	P value	Number needed to treat*
Mania/hypomania Relapse	4.6%	31.6%	p=0.036	3.7
Depressive Relapse	9.1%	21.1%	p=0.391	8.3
Overall Relapse	13.6%	42.1%	p=0.075	3.5
Days in bipolar episode (mean)	3.3	25.5	p=0.028	N/A
Insomnia Remission	63.6%	21.1%	p=0.006	2.4

Discussion: Several lines of evidence suggest that sleep disturbances contribute to mood symptoms in bipolar disorder, yet few data address the treatment of these disturbances. The results of this study support the further investigation of CBTI-BP but also suggest that psychoeducation is an active treatment that can provide at least some sleep benefits.

Study Rating*—15 (83%): This study met most criteria for a randomized controlled trial, but the source of funding was not stated.

Harvey A, Soehner A, Kaplan K, Hein K, et al: Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: a pilot randomized controlled trial. *Journal of Consulting and Clinical Psychology* 2015; doi 10.1037/a0038655. From the University of California, Berkeley; and other institutions. **Source of funding not stated. Two study authors declared financial relationships with commercial sources.**

***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.

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

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

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 have been posted at www.alertpubs.com.

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PSYCHIATRY ALERTS NOS

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Problem Adaptation Therapy in Older Patients

In a randomized trial in elderly patients with depression and cognitive impairment, problem adaptation therapy (PATH) was superior to supportive therapy at improving both mood and function.

Background: Available antidepressants have limited efficacy in older adults with depression, and most psychosocial interventions have been investigated only in ambulatory patients with mild cognitive impairment. PATH is a novel, home-delivered psychotherapy designed to reduce depression and disability in older adults with major depression. Therapy aims to improve emotion regulation and reduce the negative impact of behavioral and functional limitations. The strategies of PATH focus on 5 ways to regulate emotions: situation selection, situation modification, attentional deployment, cognitive change, and response modulation.

Methods: Study participants were 74 adults, aged 66–95 years (mean age, 81 years), with unipolar major depressive disorder, at least mild cognitive deficits, impairment in ≥1 area of daily function, and limited mobility that prevented them from attending outpatient therapy. Patients received ongoing pharmacotherapy as prescribed by their physicians. PATH combines a personalized, structured problem-solving approach, with compensatory strategies, environmental adaptations, and caregiver participation. The therapy was provided in 12 weekly home-visit sessions. The control treatment, supportive therapy for cognitively impaired older adults, was delivered in the same fashion. The primary study outcomes were improvements in depression and function, measured by blinded raters with the Montgomery-Asberg Depression Rating Scale (MADRS) and the World Health Organization Disability Assessment Schedule II (WHODAS-II), respectively.

Results: At study entry, patients had mild-to-moderate depression, pronounced disability, and significant cognitive impairment, with 52% meeting criteria for probable or definite dementia. Two-thirds were taking antidepressants. Of the 74 patients, 11 did not complete the 12 weeks of treatment; the majority because of medical hospitalization.

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PATH participants had significantly greater reductions in depression than the supportive therapy group (p=0.005 for MADRS score). Differences were evident in evaluations at weeks 4, 8, and 12, with between-group effect sizes* ranging from 0.38 to 0.79. Patients who received PATH also had significantly larger reductions in the WHODAS-II disability score (p=0.001), with effect sizes ranging from 0.36 to 0.67. The PATH group had a higher rate of remission (MADRS score of ≤7 for 2 consecutive weeks) at week 12 compared with the supportive therapy group: 38% vs. 13.5% (p=0.02; number needed to treat,* 4). They also had a higher rate of response (≥50% MADRS score reduction): 67% vs. 32% (p=0.007). Treatment satisfaction ratings did not differ between the 2 therapies.

Discussion: PATH has previously been shown to improve depression and disability in wider samples of homebound patients, including those who do not meet diagnostic criteria for depression and those with mild executive function deficits. Although treatment results were positive, additional research—by conducting booster sessions for patients who achieve partial remission—is needed to improve efficacy.

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

Kiosses D, Ravdin L, Gross J, Raue P, et al: Problem adaptation therapy for older adults with major depression and cognitive impairment: a randomized clinical trial. *JAMA Psychiatry* 2015;72 (January):22–30. From Weill Cornell Medical College, White Plains, NY; and Stanford University, CA. **Funded by the NIMH. Two study authors disclosed potentially relevant financial relationships; the remaining 4 authors declared no conflicts of interest.**

***See Reference Guide.**

Pharmacogenetic Testing in Psychiatry

Early evidence suggests that pharmacogenetic testing will contribute to important advances in treatment efficacy, tolerability, and cost-effectiveness, according to a review. Genetic testing in psychiatry has lagged behind some other areas of medicine, and there are not yet large randomized trials of its clinical and economic effects. Evidence of its utility comes from case reports and smaller studies in psychiatry and from other clinical settings.

Genetic variability among patients can lead to variations in psychotropic-treatment response and side-effect liability. Knowledge of a patient's genetic makeup can help clinicians compensate for a gene defect or adjust dosages to compensate for different rates of metabolizing drugs. For example, genes for the enzyme methylenetetrahydrofolate reductase (MTHFR), regularly tested in cancer biology, can contribute information useful in treating depression. This enzyme is involved in the synthesis of monoamine neurotransmitters. Administration of L-methylfolate has been found to be an effective augmentation strategy in patients with poor response to SSRI or SNRI treatment. Patients homozygous or heterozygous for a risk allele for MTHFR have greater responses to adjunctive L-methylfolate than patients with the normal variant. Clinical response to antidepressants and risk of side effects have also been linked to variants in the serotonin transporter protein and in hepatic cytochrome P450 enzyme pathways.

A meta-analysis found that, of 294 papers on pharmacogenetic testing in psychiatry, 57% showed positive associations between genetic variations and clinical outcomes. Testing also increases medication adherence by averting side effects or poor tolerability. Multiple cost-effectiveness studies have shown that genetic screening—to identify variations in treatment responsiveness or drug metabolism—result in lower healthcare costs.

Surveys indicate that clinicians and patients have a favorable opinion of pharmacogenomic testing. Large majorities of U.S. psychiatrists believe testing would be useful to predict serious adverse effects and to determine optimal dosages; 60% believe it would change the way psychiatry is practiced. A survey of academic psychiatrists found pharmacogenomic testing to be

most useful in cases of treatment-resistant depression and medication intolerance. Patients with chronic illnesses are open to genetic testing and feel it will contribute to the management of diseases such as depression.

Gardner K, Brennan F, Scott R, Lombard J: The potential utility of pharmacogenetic testing in psychiatry. *Psychiatry Journal* 2014; doi 10.1155/2014/730956. From Genomind, Inc., King of Prussia, PA. **Source of funding not stated. Three study authors disclosed financial relationships with commercial sources, specifically Genomind Inc.**

Proposed Eating Disorder: Orthorexia Nervosa

Orthorexia nervosa—a pathological fixation with healthy food—is an eating pattern not yet recognized as a psychiatric diagnosis but often associated with significant impairment. In orthorexia nervosa, obsessions focus on the quality or purity of food, rather than the quantity, and they manifest as a restrictive diet, a focus on food preparation (the source, processing, and packaging), and ritualized patterns of eating. Although orthorexia is motivated by concern for the individual's health, anecdotal reports suggest it may be associated with the same nutritional deficiencies as anorexia nervosa and with psychological reactions such as frustration, disgust, guilt, and chronic worry. Social isolation may ensue from feelings of moral superiority and the belief that the person can only maintain healthy eating while alone. A proposed list of diagnostic criteria include obsessional preoccupation with eating healthy foods, impairment of physical health or function, and lack of another explanation such as religion or food allergies. Symptoms of the obsessional preoccupation may include worries about impure or unhealthy foods; excessive amounts of time (>3 hours per day) involved with food-related behavior; intolerance of others' food beliefs; and spending an excessive amount of money on foods because of their perceived quality and formulation.

Orthorexia has many symptoms in common with both anorexia nervosa and OCD. Important differences are that the individual is motivated not by concern for body image, but by the desire to be "healthy, natural, or pure," often based on unrealistic beliefs about certain foods. Behaviors related to the disorder are flaunted, not hidden. Unlike OCD, the content of obsessions is ego-syntonic rather than ego-dystonic.

The prevalence of orthorexia nervosa is unknown, and estimates vary widely. The Eating Habits Questionnaire is in development and may help identify persons with a problematic focus on healthy eating. There have been no published studies of treatment for the disorder, but best-practice recommendations include the involvement of a multidisciplinary team consisting of physicians, psychotherapists, and dieticians. Therapy may be a combination of medications (SSRIs or antipsychotics, if the patient does not reject them as non-natural), cognitive behavioral therapy, and close monitoring, with hospitalization for refeeding if warranted.

Koven N, Abry A: The clinical basis of orthorexia nervosa: emerging perspectives. *Neuropsychiatric Disease and Treatment* 2015;11:385–394. From Bates College, Lewiston, ME. **Source of funding not stated. The authors declared no conflicts of interest.**

Social Skills Training for Social Anxiety Disorder

Two treatments for social anxiety disorder, exposure therapy and Social Effectiveness Therapy (SET), were equally effective in a randomized controlled trial. SET, which includes a large exposure component, was associated with additional improvements in secondary study endpoints measuring social distress and social behavior.

Background: This study was conducted to compare the 2 treatments' effects on directly observed behavioral skills, clinically significant improvement, and maintenance of treatment gains over follow-up, areas which have received little attention in previous research.

Methods: Patients (n=106) were enrolled in the study if they met diagnostic criteria for social anxiety disorder as a primary diagnosis and had been experiencing symptoms for >6 months.

Participants were randomly assigned to an active treatment or to a 12-week waiting list. SET consisted of 12 group and 12 individual sessions, each lasting 90 minutes and running concurrently over 12 weeks. Group sessions focused on social skills training, while the individual sessions provided imaginal exposure to feared scenes using a flooding format. The exposure treatment group received a similar flooding treatment, but in 2 sessions per week. The primary efficacy outcome was the proportion of responders in each group, with response defined as no longer meeting the social anxiety disorder diagnostic criteria. An alternative outcome, chosen to facilitate comparison with other clinical trials, was the proportion of patients rated much improved or better on the Clinical Global Impression—Improvement (CGI-I) scale.*

Results: At baseline, patients were markedly ill, with average CGI–Severity* ratings of 5.2. Two-thirds of the study patients completed treatment. The intent-to-treat analysis included all randomized patients. In the primary analysis, the 2 active treatments resulted in similar response rates and were superior to the wait-list control. (See table.) SET was superior to exposure therapy with regard to the CGI-I rating, the alternative endpoint. Patients who received SET also had greater improvement than the exposure group in social anxiety on the Brief Social Phobia Scale and on an observer-rated test of several anxiety-provoking behavioral tasks.

Patients meeting primary and key secondary endpoints after treatment

	SET	Exposure	Control	P value, all groups	P value, SET vs. exposure
No longer meeting diagnostic criteria	67%	54%	10%	p<0.001	NS
Effect size* vs. control	1.26	0.95	—	—	—
CGI-I much or very much improved	92%	75%	6%	p<0.0005	p<0.05
Effect size vs. control	2.68	1.61	—	—	—

Clinical significance of these results was assessed by comparing the results in each treatment group to a normative sample. Clinically significant improvement in self-reported anxiety during the behavioral tasks occurred in 97% of the SET group, 85% of the exposure group, and 14% of the controls (p<0.0005). Rates of continued response in the SET group were significantly higher than the exposure group at 3 month follow-up, but not at 6 months, at which time nearly two-thirds of each group no longer met diagnostic criteria for the disorder.

Discussion: Previous research indicates social skills training by itself is not sufficient to treat social anxiety disorder; behavior must also be addressed. The present study shows that both of the investigated exposure treatments can decrease deficits in social skills, but that specific inclusion of social skills training produces additional benefit.

Beidel D, Alfano C, Kofler M, Rao P, et al: The impact of social skills training for social anxiety disorder: a randomized controlled trial. *Journal of Anxiety Disorders* 2014;28 (December):908–918. From the University of Central Florida, Orlando; and other institutions. **Funded by the NIMH. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

SAMe Supplement Combination for Mild Depression

In a preliminary randomized trial, the combination of S-adenosyl-L-methionine (SAMe) and betaine had antidepressant efficacy at least comparable to amitriptyline in patients with relatively mild, recent-onset depression.[1]

Background: SAMe is an endogenous substance involved in the synthesis of neurotransmitters. Use can increase production of homocysteine and other toxic methylated compounds. Betaine, a cofactor in the homocysteine circuit, reduces plasma homocysteine levels and has been shown to increase plasma SAMe levels. The combination of these agents was used successfully in patients with mild depression in a previous short-term study.[2]

Method: Study participants, recruited from a single clinic in Italy, were 64 patients with moderate depression, according to the Zung Self-Rating Depression Scale (SDS), and no antidepressant drug therapy within the prior 12 months. Although recent onset was not among the entry criteria, patients had received their depression diagnosis an average of 2 months before entering the study. Participants were randomly assigned to 12 months of open-label treatment with either 250 mg SAMe plus 125 mg betaine b.i.d., or 25 mg amitriptyline t.i.d. Efficacy was evaluated at 3, 6, and 12 months. The primary outcome measure was the SDS.

Results: Four patients did not complete the study and were not included in the efficacy analysis: 2 discontinued amitriptyline because of adverse effects (i.e., sexual dysfunction and gastric pain) and 2 withdrew from SAMe–betaine for unrelated reasons.

The 2 treatments had equivalent, nonsignificant effects on depression at the 3-month evaluation. By 6 months and again at 12 months, both treatments were associated with statistically significant improvement from baseline in depressive symptoms on the SDS ($p<0.01$). SAMe–betaine was superior to amitriptyline at 6 months ($p<0.05$) and 12 months ($p<0.01$). SDS scores indicated that 15 of the 30 patients treated with SAMe–betaine were depression free at 6 months and 11 at 12 months, versus 26 and 29 patients who received amitriptyline, respectively ($p<0.01$ for all comparisons from baseline and between drugs).

Both treatments were well tolerated. According to investigator ratings, 31 patients showed good or excellent tolerability with SAMe–betaine, versus 10 patients with amitriptyline. The drugs did not differ in their effects on blood pressure, heart rate, electrocardiogram, aspartate aminotransferase, alanine aminotransferase, and body weight. (Homocysteine was not measured.)

Discussion: SAMe has previously been shown to have comparable efficacy to tricyclic antidepressants, especially when administered IM or IV or when taken orally at high doses. Persistent concerns about its cardiovascular safety prompted the present trial with betaine. The study authors could not explain the delayed response to SAMe, which does not reflect their earlier experience with the supplement.

[1]Di Pierro F, Settembre R: Preliminary results of a randomized controlled trial carried out with a fixed combination of S-adenosyl-L-methionine and betaine versus amitriptyline in patients with mild depression. *International Journal of General Medicine* 2015;8:73–78. From Velleja Research, Milan; and Di Venere Hospital, Bari, Italy. **Source of funding not stated. One study author disclosed financial relationships with commercial sources; the other author declared no conflicts of interest.**

[2]Di Pierro F, et al: Role of betaine in improving the antidepressant effect of S-adenosyl-L-methionine in patients with mild to moderate depression. *Journal of Multidisciplinary Healthcare* 2015;8:39–45.

CBT and Antidepressants in Postpartum Depression

Results of a randomized trial suggest that cognitive behavioral therapy may have modest superiority over sertraline (*Zoloft*) in women with postpartum depression. Combining the 2 therapies did not result in additional efficacy.

Methods: Women were screened for depression during a routine postnatal visit, usually 12 weeks after delivery. Those who were referred for further evaluation and met DSM-IV criteria for postnatal depression were offered randomized treatment with CBT, sertraline, or the combination of both treatments. CBT consisted of a manualized program developed by the study authors. It was provided for groups of 5–10 women in 12 weekly sessions, including 3 sessions that included the woman's partner. Sertraline was flexibly dosed in the range of 50–200 mg/day. Outcomes were assessed at baseline, after 12 weeks of randomly assigned treatment, and then again at 24 weeks, using the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Parenting Stress Index (PSI).

Results: Of 153 women who met the study's entry criteria and were offered treatment, 45 accepted randomization. Medication was never started by 4 of 14 women (29%) in the sertraline

monotherapy group and 5 of 16 (31%) in the combined therapy group. Among the women who did initiate pharmacotherapy, the average time to treatment discontinuation was 13 versus 10.5 weeks in the 2 groups, respectively. In the combination therapy group, women completed a mean of 7.5 of the 12 CBT sessions, compared with 10.6 in the CBT monotherapy group.

At the end of treatment, depression severity was decreased in all 3 treatment groups. (See table.) The 12-week BDI and BAI scores were numerically lower in the CBT monotherapy group than the other 2 groups. No significant effect of treatment on parenting stress was observed.

Treatment Outcomes			
	Baseline Mean	12 Weeks	24 Weeks
BDI			
Sertraline	29.21	19.33	19.22
CBT	27.53	12.60	11.33
Combined	31.94	24.33	17.40
BAI			
Sertraline	22.64	16.67	8.44
CBT	16.27	7.60	9.33
Combined	18.69	17.30	11.91
PSI			
Sertraline	293.82	300.43	309.75
CBT	300.92	291.11	279.38
Combined	304.92	320.50	296.50

Depression symptoms lessened earlier in treatment in the CBT group than in the sertraline or combined therapy groups. Remission (i.e., BDI score of <13) analysis showed significant improvement from baseline to week 24 only in the CBT group (p=0.007).

Discussion: This study confirms previous observations that combined therapy provides no additional efficacy over monotherapies for postpartum depression. The women receiving combination therapy had not only poorer clinical results, but lower compliance with medication and CBT. This suggests the greater time demands of combination therapy may make it less acceptable than monotherapy.

Editors' Note: Treatment adherence in the present study was low; about 30% of patients randomized to receive sertraline never started the medication, and 13% of those randomized to CBT (either alone or in combination) attended <50% of the sessions. This may have had a large impact on the statistical results of the study, particularly as the initial sample was small. In addition, the study authors did not clearly present the results of all statistical tests. Taken together, these limit the reliability of the present results. However, as the treatment effects were in the clinically desired direction, the authors suggest further research is warranted.

Milgrom J, Gemmill A, Ericksen J, Burrows G, et al: Treatment of postnatal depression with cognitive behavioural therapy, sertraline and combination therapy: a randomised controlled trial. *Australian & New Zealand Journal of Psychiatry* 2015; doi 10.1177/0004867414565474. From Heidelberg Repatriation Hospital, Australia; and other institutions. **Funded by Pfizer Inc.; and the Kinsman Fund. The authors declared no conflicts of interest.**

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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.

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

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 have been posted at www.alertpubs.com.

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Inflammatory Marker in Bipolar Disorder

According to results of a meta-analysis, there is a moderate but statistically significant association between elevated levels of C-reactive protein (CRP), an inflammatory marker, and bipolar disorder. Measurement of CRP may be clinically useful as a state or trait marker for the disorder and as a way to motivate bipolar patients toward beneficial lifestyle changes.

Methods: The meta-analysis was conducted to estimate the effect size of the known relationship between CRP elevation and bipolar disorder and to examine any possible associations with mood phase or medication. Studies were included if they were cross-sectional and comprised both patients with formally diagnosed bipolar disorder and a control group.

Results: A total of 11 studies, with 730 patients with bipolar disorder and 888 control subjects, met inclusion criteria. All were published in 2007 or later and used DSM-IV criteria for bipolar disorder. Five studies were conducted in inpatients, 4 in outpatients, and 2 in mixed samples. Most studies excluded patients with clinically significant infections or autoimmune diseases, but they varied in exclusion of patients with metabolic or cardiovascular disorders and in adjustment for confounders.

CRP levels were significantly higher overall in patients with bipolar disorder than controls (effect size,* 0.39; $p<0.0001$). CRP levels were also higher in the 188 patients experiencing a manic episode, compared with 557 controls (effect size, 0.73; $p<0.001$). CRP levels were modestly but significantly increased (effect size, 0.26) in patients with euthymia. Levels were also higher in patients with bipolar depression (effect size, 0.28), but not significantly, possibly as a consequence of small sample size. Use of lithium or antipsychotic medication was not associated with CRP levels.

Discussion: CRP is an acute-phase protein that is synthesized by hepatocytes in response to proinflammatory cytokines. Levels are elevated in cardiovascular disease and metabolic syndrome, as well as bipolar disorder. Proinflammatory cytokines are also elevated in patients with bipolar disorder, which supports the hypothesis that peripheral inflammation is a feature of this disorder. CRP may also disrupt the blood-brain barrier to allow entry of proinflam-

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matory cytokines and/or autoantibodies, supporting a causal role in neuroinflammation. In the present study, high levels in patients with euthymia indicate that CRP may be a trait marker for bipolar disorder; even higher levels in patients with mania suggest it also may be a marker for this mood state. Elevated CRP may help explain the increased risk of cardiovascular disease and metabolic syndrome in patients with bipolar disorder. Healthy lifestyle interventions—smoking cessation, diet modification, and exercise—can reduce levels of CRP and should be promoted with this aim in patients with bipolar disorder.

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

Dargel A, Godin O, Kapczinski F, Kupfer D, et al: C-reactive protein alterations in bipolar disorder: a meta-analysis. *Journal of Clinical Psychiatry* 2015;76 (February):142–150. From the Federal University of Rio Grande do Sul, Porto Alegre, Brazil; and other institutions. **Funded by the Institut National de la Sante et de la Recherche Medicale (INSERM); and other sources. Three study authors declared potentially relevant financial relationships; the remaining 2 authors declared no conflicts of interest.**

***See Reference Guide.**

Neuroanatomic Correlates of Self-Harm in Schizophrenia

Functional MRI (fMRI) studies identified differing patterns of brain activity among patients with schizophrenia and a history of self-harm, those without self-harm, and healthy control subjects. Activation of the right dorsolateral prefrontal cortex (DLPFC) was associated with suicidal thinking, which suggests this area might be a promising target for future studies of neuromodulation to prevent suicidality.

Methods: Study participants were 14 patients with schizophrenia and a history of deliberate self-harm, 14 patients with schizophrenia but no history of self-harm, and 17 healthy controls. Self-harm was assessed using a clinical interview and a review of case notes and was defined as any act—e.g., cutting, poisoning, or jumping from a height—intended to harm the subject. Participants underwent fMRI while performing the go/no-go task, which measures impulsivity and inhibition of response to a signal.

Results: All groups performed the go/no-go task with similar accuracy and reaction times. Reaction time showed higher variability in the patients with self-harm than the controls ($p<0.01$). During fMRI, 2 activity patterns differed significantly between controls and both groups with schizophrenia (i.e., they were sensitive to schizophrenia diagnosis but not to self-harm). Compared with the schizophrenia groups, the control group showed increased activation in the right ventrolateral prefrontal cortex, ventral anterior cingulate cortex, and right thalamus; and reduced activation in the right dorsal posterior cingulate cortex.

Activation of the right DLPFC and the left posterior cingulate cortex differentiated all 3 groups (i.e., was sensitive to both self-harm and to the diagnosis of schizophrenia). Activation of these areas was highest in the controls and lowest in the patients with self-harm. In the self-harm group, lower activity in the right DLPFC was correlated with poorer scores on the InterSePT Scale for Suicidal Thinking. In the group as a whole, activity in the right DLPFC was associated with more favorable scores on the Beck Hopelessness Scale and activity in the thalamus with the Deliberate Self-Harm Inventory.

Discussion: These findings suggest a role for the right DLPFC in suicide and other self-harm behaviors. Although preliminary, they also suggest neural responses may help predict suicidality and self-harm in patients with schizophrenia. Neuromodulation studies targeting the DLPFC may be warranted as a potential treatment for suicidal thinking in schizophrenia.

Lee K-H, Pluck G, Lekka N, Horton A, et al: Self-harm in schizophrenia is associated with dorsolateral prefrontal and posterior cingulate activity. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2015; doi 10.1016/j.pnpbp.2015.03.005. From the University of Sheffield, U.K. **Funded by the Sheffield Hospitals Charitable Trust. The authors declared no conflicts of interest.**

Cognitive Bias Modification for Depression

Combining positive imagery-based cognitive bias modification (CBM) with internet cognitive behavioral therapy (iCBT) conferred no additional antidepressant efficacy overall. However, among patients who completed the study protocol, those who participated in CBM experienced significantly greater improvement in depression, anhedonia, and psychological distress.

Methods: Study participants completed online screening questionnaires and then were telephoned for a diagnostic interview. Those who met criteria for a major depressive episode were randomized to receive active positive imagery CBM (n=36) or a control treatment (n=39). Both were administered in 7 computer sessions (15–20 minutes each) over the course of a week. Patients listened to scenarios that instructed them to imagine themselves in a situation that was initially ambiguous but resolved positively all of the time (positive CBM) or was evenly divided between a positive and negative resolution (control CBM). After CBM, all study subjects participated in an online CBT program, the Sadness Program, which has demonstrated efficacy in depression. Patients were evaluated and received treatment without any face-to-face contact with study personnel. Primary outcome measures, administered by blinded raters, were the Patient Health Questionnaire-9 (PHQ9), the Beck Depression Inventory (BDI), and the Ambiguous Scenarios Test for Depression (AST-D), which measures interpretation bias.

Results: The 2 groups did not differ in treatment adherence, with nearly two-thirds completing all CBM sessions and all 6 sessions of CBT. At the end of treatment, both groups showed significant improvement from baseline in depressive symptoms measured with the PHQ9 and the BDI, as well as changes in the AST-D, indicating a significant increase in positive interpretations ($p<0.001$ for all outcomes, compared with baseline). In the full sample analysis, there was no significant effect of positive CBM compared with control CBM.

However, in the per-protocol analysis of the 46 participants who completed all 7 CBM sessions, several outcomes favored active CBM. In the active CBM group, mean PHQ-9 scores decreased from 16 at baseline to 8 post-CBM, and to 7 after completion of iCBT. In the control CBM group, PHQ-9 scores were 16, 12, and 11 at the 3 time points, respectively. Compared with control treatment, the effect size* for CBM was 0.67 at end of treatment. Scores were similar in both groups at 3-month follow-up. Changes in psychological distress showed a similar pattern, and patients in the active CBM group showed significant reductions in anhedonia, while those in the control group did not. The proportions of patients experiencing clinically significant change were numerically but not statistically higher in the group receiving positive CBM. At 3-month follow-up, about half of participants—a similar proportion in both groups—no longer met diagnostic criteria for a major depressive episode.

Discussion: Based on results of their previous research, the investigators expected positive CBM to have additive effects with iCBT. The treatments may act via complementary methods—"bottom up" cognitive training (CBM) versus "top down" cognitive restructuring (iCBT). The presence of emotional ambiguity in the training scenarios and the use of imagery, elements possibly crucial to the effects of CBM, were present in both the positive and control treatments, which may underlie the lack of between-group differences. Additional study using a control intervention that does not incorporate components of CBM appears to be warranted.

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

Williams A, O'Moore K, Blackwell S, Smith J, et al: Positive imagery cognitive bias modification (CBM) and internet-based cognitive behavioral therapy (iCBT): a randomized controlled trial. *Journal of Affective Disorders* 2015;178 (June):131–141. From the University of New South Wales, Sydney, Australia; and other institutions. **Funded by the University of New South Wales; and other sources. One study author disclosed potentially relevant financial relationships; the remaining 5 authors declared no conflicts of interest.**

***See Reference Guide.**

Smartphone Sensors for Mental Health Monitoring

Identification of warning signs that are potentially associated with worsening mental health could facilitate early intervention and improved outcomes. Results of a proof-of-concept experiment suggest that clinically useful psychiatric monitoring to target time-sensitive interventions could be carried out using smartphones with minimal burden to patients.

Methods: A total of 47 college undergraduate and graduate students participated in a 10-week study. They were given an Android smartphone and instructed to carry it with them throughout the study period, recharging it while they slept. Data for the analysis were obtained from the phones' built-in microphone, accelerometer, light sensor, and GPS. Using software written for the project, the phones recorded virtually continuously and analyzed the data to record speech duration (the proportion of the day in which the individual spoke or was near someone speaking), geospatial movement, physical activity, and sleep duration. The phones also prompted participants to record their stress levels at intervals throughout each day. At the beginning and end of the study, participants completed questionnaires on stress (Perceived Stress Scale), depression (Patient Health Questionnaire-9), and loneliness (Revised UCLA Loneliness Scale). The investigators analyzed the relationship between sensor data and daily stress, as well as pre- and post-study differences in the 3 indicators of mental health.

Results: Daily stress was associated with both decreased sleep duration (p=0.05), decreased geospatial activity (p=0.03), and decreased within-individual variation in geospatial activity (p=0.05). Several significant associations with sensor data were observed, with variation over time. For example, increased speech duration was associated with more favorable changes in depressive symptoms when it occurred early in the study, and greater increases in depressive symptoms when it occurred later (p=0.05). Increased geospatial activity and increased sleep duration showed a time-varying relationship with depression. Kinesthetic activity was associated with changes in perceived loneliness over time, with higher scores later in the study strongly associated with less loneliness (p=0.002). No relationships were found between any sensor data and longitudinal changes in perceived stress.

Discussion: Previous research has already identified relationships between activity, sleep, social context, and mental health. The present study demonstrates that these variables can be measured remotely, without submitting the individual to interviews, self-reports, or clinic visits. Further mobile health (mHealth) research should examine whether smartphone data can be used to predict impending clinical problems, such as a relapse of schizophrenia or mania.

Study Rating*—12 (86%): This study met most criteria for an observational study, but the source of funding was not stated.

Ben-Zeev D, Scherer E, Wang R, Xie H, et al: Next-generation psychiatric assessment: using smartphone sensors to monitor behavior and mental health. *Psychiatric Rehabilitation Journal* 2015; doi 10.1037/prj0000130. From Dartmouth College, Lebanon, NH. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

Dialectical Behavior Therapy for Suicide Risk

In a randomized trial, incorporating the skills training component of dialectical behavior therapy (DBT) resulted in better acute outcomes in a group of women with borderline personality disorder.

Background: Multicomponent DBT has evidence-based support for efficacy in borderline personality disorder. However, demand for DBT exceeds its availability. The components of the therapy are often offered individually in clinical settings. This trial was undertaken to assess the importance of the skills training component of DBT.

Methods: Women (n=99) with borderline personality disorder at high risk of suicide based on multiple recent suicide attempts or episodes of nonsuicidal self-injury (NSSI) were randomized to 1 year of treatment with standard DBT, DBT with skills training (DBT-S), or DBT individual therapy (DBT-I). Standard DBT included both individual therapy and group skills training. For DBT-S, the individual therapy component was removed, and, to control for treatment dose and to ensure crisis/suicide management, patients received a manualized case management intervention. For DBT-I, group skills training was removed and therapists were not allowed to teach any new DBT skills, only to help patients use the skills they already had. An activity-based support group was added to DBT-I to control for treatment dose. All therapists were trained in the Linehan Suicide Risk Assessment and Management Protocol (LRAMP) of DBT. The primary study outcome was incidence of suicidal attempts and NSSI, measured with the Suicide Attempt Self-Injury Interview. Other evaluations included the Reasons for Living Inventory, use of crisis services, and Hamilton Rating Scales for Anxiety and Depression. Outcomes were assessed quarterly during 1 year of therapy and 1 year after the end of treatment.

Results: Overall, suicide-related outcomes differed little among the 3 treatment groups. One patient in the standard DBT group committed suicide, more than a year after dropping out of therapy. There were no significant between-group differences in the occurrence of suicide attempts; the frequency or medical risk of suicide attempts among attempters; the occurrence or medical risk of NSSI episodes; or the secondary outcomes of suicidal ideation, reasons for living, or emergency-department visits or hospitalizations for suicidality. However, during the treatment year, interventions that included skills training resulted in a lower frequency of NSSI. In addition, depression and anxiety improved significantly more in the groups that received skills training than in the DBT-I group. By the 1-year follow-up, however, improvement in the DBT-I group had caught up with the other groups.

Discussion: It is difficult to generalize the results of this study because of a high dropout rate, the suicide expertise conferred by training in LRAMP, and the enforcement on all practitioners of monitoring suicide risk. However, the results suggest DBT programs that include skills training may have advantages over protocols that do not include skills training, at least during acute treatment.

Linehan M, Korslund K, Harned M, Gallop R, et al: Dialectical behavior therapy for high suicide risk in individuals with borderline personality disorder: a randomized clinical trial and component analysis. *JAMA Psychiatry* 2015; doi 10.1001/jamapsychiatry.2014.3039. From the University of Washington, Seattle; and other institutions. **Funded by the NIMH. Five study authors declared potentially relevant financial relationships; the remaining 4 authors declared no conflicts of interest.**

PTSD Treatments in Patients with Psychosis

It has been estimated that 1 in 8 patients with a psychotic disorder has comorbid PTSD; however, these patients are often excluded from treatment trials. According to the results of a randomized trial, prolonged exposure (PE) therapy and eye movement desensitization and reprocessing (EMDR) therapy, the recommended first-line therapies for PTSD, are effective in these patients.

Methods: Study participants (n=155), recruited from Dutch outpatient clinics for severe mental disorders, were adults with a lifetime diagnosis of a psychotic disorder or a mood disorder with psychotic features. All patients met DSM-IV-TR criteria for chronic PTSD. Participants were randomly assigned to PE, EMDR, or a wait-list control condition. Both active treatments were delivered in 8 weekly 90-minute sessions based on published standard protocols. Patients continued with medication and other therapies for psychosis, but they were not allowed to start any new trauma-focused therapy during the trial. Efficacy was assessed with the Clinician-Administered PTSD Scale (CAPS) at the end of treatment and 6 months later. Full remission was indicated by a CAPS total score <20.

Results: At baseline, study participants were characterized by severe posttraumatic, psychotic, and depressive symptoms, and most had a history of multiple childhood traumatic exposures. The 2 active treatments were equivalent to one another and superior to control in reducing the severity of PTSD symptoms. (See table). Improvements observed at the end of treatment persisted at 6-month follow-up.

At the 8-week post-treatment evaluation, significantly more patients in the active treatment groups no longer met diagnostic criteria for PTSD: 57% of the PE group and 60% of the EMDR group, compared with 28% of the wait list group ($p \leq 0.001$). The numbers needed to treat* for 1 patient to no longer meet diagnostic criteria were 3.5 and 3.1 in the PE and EMDR groups, respectively. Full remission was achieved by 28% of the PE group, 16% of the EMDR group, and 6% of the wait-listed patients. Results were similar, but attenuated slightly, at 6-month follow-up.

Treatment Outcomes Following PE or EMDR vs. Wait List

	PE	EMDR	Wait List
Baseline CAPS Score	69.6	72.1	68.1
Post-Treatment CAPS Score	37.8	40.3	56.5
Effect Size*	0.78	0.65	NA
Significance vs. Wait List	p<0.001	p=0.001	NA
6-Month CAPS Score	36.7	38.8	51.9
Effect Size	0.63	0.53	NA
Significance vs. Wait List	p=0.002	p=0.009	NA

Participants were allowed to complete treatment before its scheduled end if they had low self-reported PTSD symptoms and distress on 2 consecutive treatment visits. Eight patients in the PE group and 2 in the EMDR group were early completers. Rates of premature treatment discontinuation were 25% for PE and 20% for EMDR.

Discussion: Research has shown that many clinicians are reluctant to treat PTSD in patients with psychosis, partly out of fear of exacerbating the illness. Results of the present study should be applicable to routine clinical practice because standard treatment protocols were used and the study population was selected with few exclusion criteria.

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

van den Berg D, de Bont P, van der Vieugel B, de Ross C, et al: Prolonged exposure vs eye movement desensitization and reprocessing vs waiting list for posttraumatic stress disorder in patients with a psychotic disorder: a randomized clinical trial. *JAMA Psychiatry* 2015;72 (March):259–267. From Parnassia Psychiatric Institute, Den Haag, the Netherlands; and other institutions. **Funded by the Stichting tot Steun VCVGZ, a Dutch support foundation. Five study authors declared potentially relevant financial relationships; the remaining 2 authors declared no conflicts of interest.**

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Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect.

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

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 have been posted at www.alertpubs.com.

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Mindfulness-Based Therapy as Depression Maintenance

In a randomized trial in patients with recurrent major depression, relapse-prevention outcomes were similar with mindfulness-based cognitive therapy (MBCT) and maintenance antidepressant pharmacotherapy. MBCT could provide cost-effective protection for patients who would like an alternative to maintenance drug therapy.

Methods: Study subjects, recruited from primary-care practices in the U.K., had a diagnosis of recurrent major depression (≥3 prior episodes) in full or partial remission and were receiving ongoing maintenance antidepressants. Patients were randomly assigned to continue drug therapy for 2 years or to switch to MBCT with support to taper antidepressants. MBCT is a manualized, group-based program that teaches patients to be more aware of their bodily sensations, thoughts, and feelings associated with depressive relapse and how to respond adaptively to depression triggers. The program was delivered in about 8 sessions, lasting 2.5 hours each, over consecutive weeks, plus 4 booster sessions over the following year. The primary outcome was relapse or recurrence, defined as meeting DSM-IV criteria for a major depressive episode. Economic costs of the treatments, including health care, social services, and productivity loss, were also compared.

Results: A total of 424 patients from 95 primary medical practices were randomized. Primary outcome data were available for about 90% of patients. Outcomes in both treatment groups were relatively good, given these patients' high risk of recurrence. MBCT was not associated with significantly reduced risk of relapse compared with maintenance antidepressants (hazard ratio,* 0.89). During the 2 years, 44% of the MBCT patients and 47% of the medication group experienced a relapse. MBCT was superior to medication in a separate analysis of patients with high severity of childhood abuse: 47% relapse rate with MBCT and 59% with medication. Patients with abusive childhoods had a generally poorer course of disease before the current episode, with more depressive episodes, treatments, hospitalizations, and suicide attempts. Average overall costs in the MBCT group exceeded costs in the medication group by approximately $195, the amount of MBCT group attendance for 1 patient.

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Discussion: The finding that MBCT is more effective in higher-risk patients is consistent with previous research. MBCT may confer resilience in patients at high risk by teaching skills that address underlying mechanisms of relapse.

Kuyken W, Hayes R, Barrett B, Byng R, et al: Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): a randomised controlled trial. *Lancet* 2015; doi 10.1016/S0140-6736(14)62222-4. From the University of Oxford, U.K.; and other institutions. **Funded by the National Institute for Health Research Health Technology Assessment program. Two study authors declared potentially relevant relationships with commercial sources; the remaining 24 authors declared no conflicts of interest.**

***See Reference Guide.**

Transcutaneous Vagus Stimulation for Depression

In a preliminary trial, transcutaneous vagus nerve stimulation (tVNS) applied to the ear relieved symptoms in a group of patients with mild or moderate depression. Treatment success was associated with changes in functional connectivity in brain regions involved in emotional modulation.

Background: VNS with surgically implanted electrodes is an FDA-approved treatment for refractory depression. The present study evaluated a new noninvasive technique that was expected to produce a similar effect, without the risks and burden of surgery. The rationale for using tVNS is that the ear is the only place on the surface of the body with afferent vagus nerve distribution.

Methods: Study participants (aged 16–70 years; n=49) had been experiencing depressive symptoms for ≥2 months but not longer than 2 years. All had discontinued prior antidepressant treatment ≥2 weeks before study entry. The initial cohort of patients received active tVNS, and once the effect was established, a second cohort who received sham tVNS in a single-blind fashion was included. Patients administered the treatment to themselves at home, using clips attached to the ear at the stimulation site. The stimulus was adjusted to 20 Hz with a wave width <1 ms and intensity adjusted between about 4 and 6 mA based on patient tolerance. For the 4-week duration of the trial, treatment was administered for 30 minutes, twice a day, at least 5 days per week. The primary endpoint was change on the 24-item Hamilton Rating Scale for Depression (HAM-D). Patients underwent functional magnetic resonance imaging (fMRI) scanning before and after treatment.

Results: Of the 49 patients recruited for the trial, 35 completed the 2 fMRI scans. The mean HAM-D score decreased from 28.5 points before treatment to 15 with tVNS and to 23 with sham treatment (p=0.002). Active treatment was also associated with significant decreases relative to sham treatment in the Self-Rating Depression Scale (p=0.01) and the Self-Rating Anxiety Scale (p=0.01), but not the Hamilton Anxiety Rating Scale.

Pre- and post-treatment fMRI scans showed significant differences in functional connectivity in brain regions of interest in the 2 groups. A positive association was evident between changes in HAM-D score during treatment and changes in functional connectivity between the default mode network and the left orbital prefrontal cortex, middle occipital gyrus, and other structures. Changes in HAM-D severity were inversely correlated with changes in functional connectivity between the default mode network and the bilateral dorsal lateral prefrontal cortex, parahippocampus, and other structures.

Discussion: Brain imaging studies have demonstrated that depression is associated with abnormalities in brain circuits involved in emotional processing, self-representation, reward, and stress interactions. These brain regions—including the hippocampus, amygdala, anterior cingulate cortex, and medial prefrontal cortex—are within the default mode network of the

brain, which is active when the individual is at rest, not focused on the outside world. Functional connectivity of the default mode network may be a useful tool in understanding the underlying mechanisms of depression treatment.

Study Rating*—15 (88%): This study met most criteria for a controlled trial; however, treatment assignment was not random.

Fang J, Rong P, Hong Y, Fan Y, et al: Transcutaneous vagus nerve stimulation modulates default mode network in major depressive disorder. *Biological Psychiatry* 2015; doi 10.1016/j.biopsych.2015.03.025. From the China Academy of Chinese Medical Sciences, Beijing; and other institutions. **Funded by the National Science Foundation of Beijing China; and other sources. The authors declared no conflicts of interest.**

***See Reference Guide.**

Long-Term VNS in Mood Disorders

Vagus nerve stimulation can be an effective, adjunctive, long-term maintenance treatment for refractory depression, according to a report on a small series of patients followed for ≤5 years.

Methods: Study patients (n=5) had a chronic current major depressive episode—i.e., lasting ≥2 years or having had >4 lifetime episodes—and had not experienced response with ≥2 prior antidepressant trials. They received treatment at a tertiary referral hospital specializing in mood disorders. All patients were receiving antidepressants, with or without mood stabilizers. Baseline medications were continued for at least a year after stimulator implant surgery, with dosage adjustments as indicated. Patients were assessed every 3 months for the first 2 postoperative years and then annually. Response was defined as a ≥50% decrease from baseline on the Hamilton Rating Scale for Depression (HAM-D), and remission as a score of ≤7.

Results: At baseline, participants had a mean age of 57 years (range 48–66 years) and a mean HAM-D score of 23. Three had chronic unipolar major depression, and 2 had bipolar disorder with >10 lifetime episodes of major depression. Three had a history of suicide attempts. Study patients had used a mean of 8 different antidepressants from >3 drug classes before trying VNS and were receiving an average of 3 medications at the time of the implant.

At 12 months, the mean HAM-D score was decreased to 15 and the response rate was 40%. Maintenance VNS was successful in 3 patients who remained in follow-up and continued using the VNS devices for 5 years. Of these, 2 experienced remission late in the first year and the third during the second year. One patient was free of recurrence for the entire time after the initial episode resolved, and the others each had a single recurrence during the fourth year. Another patient had slight improvement in depression but withdrew from the study after 18 months and had the generator switched off, citing intolerable hoarseness, sore throat, and neck pain. The final patient withdrew after a year with unchanged depression severity, even after receiving advice that VNS effects are sometimes not seen until after 12 months.

Discussion: VNS has not been shown to have rapid antidepressant effects and may therefore not be useful as an acute treatment. Positive effects are often not seen until after ≥3 months of therapy, and as seen in this series of patients, there is a progressive decline in symptoms over the first year of treatment. However, little has been known about the long-term efficacy as there have been very few reports that followed patients for as long as 5 years. The present report confirms previous suggestions that VNS is effective in a small but significant proportion of patients whose depression is unresponsive to other treatments. It also appears to reduce exacerbations over the long term in the vast majority of those who achieve response.

Albert U, Maina G, Aguglia A, Vitalucci A, et al: Vagus nerve stimulation for treatment-resistant mood disorders: a long-term naturalistic study. *BMC Psychiatry* 2015; doi 10.1186/s12888-015-0435-8. From the University of Torino, Italy. **Source of funding not stated. The authors declared no conflicts of interest.**

Excess Cancer Mortality in Psychiatric Patients

According to results of an Australian population-based cohort study, patients with a psychiatric illness have a similar cancer incidence but higher cancer mortality than the general population. The differences cannot be easily explained.

Methods: Members of the psychiatric patient cohort were identified through medical record review as individuals who had contact with a health service for a psychiatric diagnosis, including postpartum mental disorders and suicide attempts, or who had any contact with the mental health system. Cases of cancer and cancer deaths were ascertained between 2002 and 2007. Cancer incidence and mortality in the cohort were compared with the general population using age- and gender-standardized rates and adjustment for multiple confounders.

Results: Nearly 90,000 new cases of cancer were identified in Queensland, including about 3300 in patients with mental illness. Overall cancer incidence was slightly lower for psychiatric patients than the general population (rate ratio,* 0.94). Patients with mental illness had lower rates for most of the major cancer sites—prostate, breast, colorectal, and melanoma—as well as for uterine, thyroid, and urinary-tract cancers. They had higher rates of lymphoma as well as lung, mouth, esophagus, and liver cancers. Patients with alcohol and substance-use disorders and those with a history of inpatient treatment had elevated rates of cancer, and those with dementia or schizophrenia had a reduced risk of cancer. Overall mortality in patients with mental illness and cancer was 41% higher than the general population with cancer (adjusted hazard ratio,* 2.27).

Discussion: The physical health of psychiatric patients has attracted increasing attention in the past decade. Cancer has received less attention than some other causes, which is surprising given psychiatric patients' higher rates of smoking, and alcohol and substance use, as well as the hyperprolactinemia that is associated with antipsychotics. Studies of cancer incidence and mortality in the mentally ill have had conflicting results. In this study, psychiatric patients had higher rates of more advanced cancers at diagnosis. Other research has suggested that patients with mental illness have reduced access to cancer surgery. The advanced stage at diagnosis and lack of access to surgical interventions may be responsible, at least in part, for the greater mortality associated with cancer in the psychiatric-patient population. Multipronged approaches will likely be needed to address these inequalities.

Kisely S, Forsyth S, Lawrence D: Why do psychiatric patients have higher cancer mortality rates when cancer incidence is the same or lower? *Australian & New Zealand Journal of Psychiatry* 2015; doi 10.1177/0004867415577979. From the University of Queensland, Herston, Australia. **Funded by Cancer Council Queensland. The authors declared no conflicts of interest.**

***See Reference Guide.**

Measuring Functional Outcomes in Depression

According to a consensus statement from the Canadian Network for Mood and Anxiety Treatments (CANMAT), functional assessment should be routinely conducted in addition to symptom assessment in the clinical care of patients with major depressive disorder (MDD).

Functional recovery is now being recognized by both physicians and patients as a priority in the treatment of MDD. Functioning (not to be confused with quality-of-life) refers to a patient's ability to perform daily tasks and to engage in relationships with others that are gratifying and that meet the needs of both the individual and the community. These outcomes are measured using either objective or subjective assessment of performance in ≥1 behavioral domains, such as family, social, or occupational functioning. (See table for examples of validated measures.) Functional outcomes often are cited by patients as more important than symptom relief.

However, symptom improvement remains the focus of traditional clinical trials for MDD, even though functional outcomes in MDD only are moderately associated with symptom relief. Functional recovery in patients with MDD can lag behind symptomatic or syndromal recovery, and even mild or subthreshold symptoms are associated with compromised functioning. Restoration of functioning can occur in 1 domain but remain impaired in another.

Validated Functional Outcome Assessment Scales for MDD		
Scale	**Functional Domain(s) Assessed**	**Format**
Canadian Occupational Performance Measure	Global/occupational	Clinician-administered
Sheehan Disability Scale	Global/multi-domain	Self-report
Global Assessment of Functioning	Global	Clinician-administered
Social Adaptation Self-evaluation Scale	Social	Self-report
Social Adjustment Scale—Self-Rated	Social	Self-report or clinician-administered
Social and Occupational Functioning Assessment Scale	Global	Clinician-administered
World Health Organization Psychiatric Disability Assessment Scale	Social	Clinician-administered
World Health Organization Health and Work Performance Questionnaire	Occupational	Self-report
Endicott Work Productivity Scale	Occupational	Self-report
Lam Employment Absence and Productivity Scale	Occupational	Self-report
Stanford Presenteeism Scale	Occupational	Self-report
Work Limitations Questionnaire	Occupational	Self-report
Work Productivity and Activity Impairment	Occupational	Self-report
Work and Social Adjustment Scale	Occupational and social	Self-report

Functional assessments, if they are completed at all, are usually secondary outcomes. To date, there is no gold standard tool for measuring functional capacities. Available measures of function generally require <5 to <30 minutes to complete and are recommended by the CANMAT consensus team as a necessary component in the comprehensive management of MDD.

Lam R, Parikh S, Michalak E, Dewa C, et al: Canadian Network for Mood and Anxiety Treatments (CANMAT) consensus recommendations for functional outcomes in major depressive disorder. *Annals of Clinical Psychiatry* 2015;27 (May):142–149. From The University of British Columbia, Vancouver; and the University of Toronto, Canada. **Funded by CANMAT; and RxD Research Foundation. Three study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

Advances in Understanding, Treating Hoarding Disorder

Recognition of hoarding disorder as a discrete diagnosis has fueled a surge of research into its psychology, neurobiology, and treatment. Inclusion of hoarding disorder as a separate disorder in DSM-5 has been a critical step forward.

Historically, pathologic hoarding was considered a feature of obsessive-compulsive disorder (OCD) or obsessive-compulsive personality disorder. Recent studies that focused on a more specifically defined patient population and used newly developed clinical measures support it as a distinct diagnostic entity.

According to a widely accepted model of the disorder, the core features—acquiring, clutter, and difficulty discarding—arise from emotional attachment to possessions, avoidance behaviors resulting from the emotional distress of discarding them, and deficits in attention, categorization, memory, and decision making. Hoarding behaviors allow the patient to both avoid distress and feel comfort, likely maintaining the disorder through simultaneous positive and negative reinforcement. In addition, patients who hoard are distractible, have difficulty with sustained and spatial attention, and have a high prevalence of ADHD symptoms. Patients with hoarding disorder tend to have not only memory deficits, but also poor confidence in their memories, leading them to keep their possessions in sight to avoid forgetting them. They also often have an exaggerated estimation of the negative consequences of forgetting. The disorder is also associated with deficits in executive functioning, marked by inability to organize and categorize belongings, indecision, and difficulty completing tasks.

Brain imaging and EEG studies of patients with hoarding disorder have identified deficits in the anterior cingulate cortex and related areas, which may underlie both difficulty in making decisions and overwhelming emotions. Hoarding disorder is also associated with abnormal activation in the precentral and superior frontal gyri, associated with complex behavior and motor control.

Recent evidence suggests that a form of cognitive behavioral therapy (CBT) specifically adapted for hoarding disorder may be effective. The manualized treatment program includes education about hoarding and improving decision-making skills; developing a system to organize possessions; graded exposure to the anxiety and distress associated with classifying, discarding, and placing possessions out of sight; and cognitive restructuring. In controlled studies, CBT was associated with moderately large effect sizes measured with the Saving Inventory-Revised (SI-R), although there is considerable room for improvement. Novel interventions currently under investigation include computer-assisted cognitive remediation, Web-based CBT, and bibliotherapy-based self-help groups. Pharmacotherapy trials for hoarding disorder have had inconsistent results, in part because of poor diagnostic specificity in patient samples, use of OCD rating scales rather than the SI-R, and poor treatment adherence. However, preliminary studies indicate extended-release venlafaxine and other SNRIs may be as effective as CBT. Patients with ADHD symptoms have had improvement in both ADHD and hoarding after treatment with methylphenidate, but gains were small and the treatment was not well accepted.

Grisham J, Baldwin P: Neuropsychological and neurophysiological insights into hoarding disorder. *Neuropsychiatric Disease and Treatment* 2015; 11:951–962. From the University of New South Wales, Sydney, Australia. **Funded by a fellowship from the university; and other sources. The authors declared no conflicts of interest.**

Drug Trade Names*: methylphenidate—*Ritalin*; venlafaxine—*Effexor

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

Rate Ratio: A comparison of the rates of a disease/event in 2 groups that differ by demographic characteristics or exposure history. The rate for the group of primary interest is divided by the rate for a comparison group.

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

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Adjunctive CoQ10 in Geriatric Bipolar Depression

In an open-label proof-of-concept study, coenzyme Q10 was effective as adjunctive therapy in a group of older adults with bipolar depression.

Background: Evidence is accumulating that alterations in bioenergetic metabolism and enhanced oxidative stress may have a role in the neurobiology of bipolar disorder. In addition, the efficiency of mitochondrial energy production declines with age. As a result, successful treatment of late-life bipolar disorder may require strategies that focus on ways to address reduced mitochondrial adenosine triphosphate production. CoQ10 has been studied as a treatment for other disorders associated with mitochondrial impairment, including congestive heart failure, diabetes, and degenerative neurological conditions.

Methods: Study patients were 19 adults, aged ≥55 years (mean age, 63 years), with type 1 or 2 bipolar disorder who were experiencing a current depressive episode. In addition to existing pharmacotherapy, all subjects received CoQ10 at 400 mg/day for 2 weeks and then titrated to 800 mg day for an additional 2 weeks. The primary efficacy measure was the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: The mean baseline MADRS score of 24 indicated moderate depression in the sample as a whole. The mean Young Mania Rating Scale score of 4.3 indicated low manic symptom severity. Patients experienced improvements in depression that were evident at the first post-baseline assessment (2 weeks). After adjustment for age, gender, and statin use, the improvement at 2 weeks was marginally significant (p=0.07) and strengthened by the fourth study week (p=0.001). Analysis of specific symptom domains showed a significant decline in the retardation factor, which includes lassitude, apparent sadness, inability to feel, and concentration difficulty. CoQ10 was well tolerated. A single patient withdrew from the study due to diarrhea that resolved with CoQ10 discontinuation. There were no other reported medication-associated adverse effects.

Forrester B, Harper D, Georgakas J, Ravichandran C, et al: Antidepressant effects of open label treatment with Coenzyme Q10 in geriatric bipolar depression [letter]. *Journal of Clinical Psychopharmacology* 2015;35 (3):June: 338–340. From McLean Hospital Belmont; and Harvard Medical School, Boston, MA. **One study author disclosed financial relationships with commercial sources; the remaining 5 authors declared no conflicts of interest.**

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Gender-Specific Effects of SAMe

Men and women with major depressive disorder may experience different responses to S-adenosyl methionine (SAMe), according to a secondary analysis of clinical trial data.[1]

Background: The randomized controlled trial upon which this analysis was based found no significant differences in efficacy among SAMe, placebo, and escitalopram (*Lexapro*) in patients with major depressive disorder.[2] However, because there was a significant difference between the 2 study sites in the proportion of male patients (59% vs. 31%), this gender-based post-hoc analysis was undertaken to determine if response differed by gender.

Methods: Study participants were 189 outpatients, aged 18–80 years, with major depression (DSM-IV) and a score of ≥25 on the Inventory of Depressive Symptomatology (Clinician Rated). Patients received 12 weeks of randomly-assigned, double-blind SAMe, escitalopram, or placebo. The 17-item Hamilton Rating Scale for Depression (HAM-D) was used as the primary outcome measure. The present analysis, conducted by the same investigators, examined the main outcome separately in men (n=51) and women (n=62) who received either SAMe or placebo.

Results: Mean baseline HAM-D scores were about 20 points in men and 19 points in women. Among the male patients, the mean HAM-D-17 score was reduced by 8.9 points in the SAMe group at 12 weeks, compared with a decrease of 4.6 points in the placebo group (p=0.034; effect size,* 0.95). In the women, change in HAM-D score did not differ significantly between the groups: 5.4 points with SAMe and 6 points with placebo. Gender did not appear to affect response rates (≥50% HAM-D reduction).

Discussion: SAMe is a component of the one-carbon cycle, involved in the methylation of neurotransmitters responsible for mood regulation. Previous research has suggested it may be effective as augmentation in patients with partial response to SSRIs or SNRIs, and clinical studies provide several lines of evidence that support possible mechanisms for a gender-specific effect on SAMe in depression. The present study is limited by its post-hoc nature, and prospective studies are needed to determine if the results can be replicated.

[1]Sarris J, Price L, Carpenter L, Tyrka A, et al: Is S-adenosyl methionine (SAMe) for depression only effective in males? A re-analysis of data from a randomized clinical trial. *Pharmacopsychiatry* 2015; doi 10.1055/s-0035-1549928. From the University of Melbourne, Richmond, Australia; and other institutions. **Funded by the NIH; and the National Center for Complementary and Alternative Medicine. One study author declared potentially relevant financial relationships with commercial sources.**

[2]Mischoulon D, et al: A double-blind, randomized, placebo-controlled clinical trial of S-adenosyl-L-methionine (SAMe) versus escitalopram in major depressive disorder. *Journal of Clinical Psychiatry* 2014;75:370–376.

***See Reference Guide.**

Bright Light Therapy for Depression

In a randomized trial, adding bright light therapy to venlafaxine (*Effexor*) treatment resulted in earlier and more robust improvement in inpatients with severe depression.

Background: Bright light therapy is believed to exert mood-elevating effects via monoaminergic and circadian system-associated melatonergic mechanisms, and it is known to effectively augment SRI therapy in mild-to-moderate depression. This study appears to be the first to evaluate the effects of bright light therapy in a severely affected population and as an adjunct to an SNRI.

Methods: Study participants were 50 patients (mean age, 36 years; 27 women) with a new diagnosis of major depression who were receiving inpatient treatment because of the

severity of their symptoms. All patients received treatment for 8 weeks with a morning dose of venlafaxine, initiated at 75 mg/day for the first week, and then increased to 150 mg/day for weeks 2–8. A total of 25 randomly selected patients also received bright light therapy: 7000 lux for 1 hour, beginning at 7 AM, for the first week of the study. Efficacy was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D), with scores of ≤13 indicating remission of severe depression but continued mild depression and ≤7 indicating complete recovery (i.e., absence of depression).

Results: Both groups showed significant improved with treatment. At week 2, HAM-D scores were reduced to a significantly greater degree with adjunctive bright light therapy. This group also had significantly higher rates of severe-depression remission at week 4, but rates of complete recovery at week 8 were similar in both groups.

Selected Patient Outcomes			
	Venlafaxine (n=25)	**Venlafaxine plus Bright Light Therapy (n=25)**	**Significance**
Mean HAM-D at Baseline	29.3	29.9	N/A
Mean HAM-D at Week 2	19.2	15.4	p=0.018
Mean HAM-D at Week 8	7.4	5.7	p=ns
Remission (HAM-D ≤13) at Week 4	44%	76%	p<0.05
Complete Recovery (HAM-D ≤7) at Week 8	64%	76%	p=ns

The Profile of Mood States scale, a secondary outcome measure, showed improvements in the total score and in several subscales that were larger at 2 weeks with bright light therapy than venlafaxine alone: depression-dejection, tension-anxiety, anger-hostility, confusion-bewilderment, and fatigue-inertia ($p<0.025$ for all). Most of these differences remained significant at week 8. The known adverse effects of bright light therapy, such as headache, eyestrain, and fatigue, were not reported by patients in this study.

Discussion: Therapeutic response to antidepressants often requires 4–6 weeks of treatment. Results of this study suggest that adding bright light therapy may speed response in patients with severe depression.

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

Ozdemir P, Boysan M, Smolensky M, Selvi Y, et al: Comparison of venlafaxine alone versus venlafaxine plus bright light therapy combination for severe major depressive disorder. *Journal of Clinical Psychiatry* 2015;76 (May):e645–e654. From Yuzuncu Yil University, Van, Turkey; and other institutions. **Funded by Yuzuncu Yil University. The authors declared no conflicts of interest.**

***See Reference Guide.**

Improving Medication Compliance in Schizophrenia

As many as half of patients with schizophrenia who experience response with pharmacotherapy do not adhere to their medication regimens, which can lead to poor outcomes. Many factors affect medication adherence, including patient perceptions about illness and medication; symptom severity; level of cognitive function and insight; adverse effects; patient age; and comorbid medical illnesses. A systematic review of research conducted in the past decade identified support-service interventions to promote adherence, which clinicians should address as a priority in patients with schizophrenia.

The essential first step in improving adherence is to establish a trusting therapeutic relationship with the patient. Prescribers should work with the patient to determine causes for nonadherence and target patient-specific support strategies. Prescribers can use cognitive strategies to link adherence to the patient's treatment goals, such as staying out of the hospital, living independently, or returning to work or school. Patients should be routinely included in decisions about medications, and their knowledge and attitudes should be assessed throughout the provision of support services.

According to the literature, there are 3 main types of intervention to improve medication adherence: support and education; technological approaches; and motivational interviewing. The investigators reviewed clinical trials of these and other approaches published over the past 10 years. Of 22 studies reviewed, 11 reported significant improvement in medication adherence.

Studies of support service and education interventions (n=7) had varying results. A family support program that trained family members to be key supervisors of medication adherence had positive results on adherence, as did a culturally-adapted multifamily program tailored to Spanish-speaking Mexican-Americans. Five studies examined clinician support and education programs, in which clinicians provided special face-to-face sessions focusing on compliance issues. Of these, only 1 showed an improvement in medication adherence, and this improvement was transient.

The use of technology to improve compliance has been investigated in 5 clinical trials. Services such as text messaging or telephone reminders were generally effective, although in 1 study adherence returned to baseline once the text messages were discontinued. In a study of electronic pill counters, adherence improved in patients who were already relatively adherent at baseline, but not in those who were nonadherent. A computerized system that alerted clinicians when patients reported psychotic symptoms via an electronic message did not improve medication adherence.

Motivational interviewing in conjunction with treatment adherence therapy (TAT) or problem-solving approaches has been evaluated in 4 studies. Effective approaches of this type consisted of multiple sessions spanning 8 weeks to 6 months. In 1 study, motivational interviewing was not more effective than health education in raising adherence. Effective approaches included TAT, which combines motivational interviewing with medication optimization and behavioral training, and clinical interviews with a registered nurse that identified and addressed barriers to adherence. Another effective approach was adherence therapy, which focused on beliefs about medication and problem solving.

A variety of other support interventions have also been investigated. A multifaceted program that included cognitive behavioral therapy did not improve compliance. Effective approaches included modest financial incentives, a pharmacy-based intervention, and environmental supports—consisting of home visits and adaptation of the home environment to incorporate cues to keep appointments and take medication.

El-Mallakh P, Findlay J: Strategies to improve medication adherence in patients with schizophrenia: the role of support services. *Neuropsychiatric Disease and Treatment* 2015;11:1077–1090. From the College of Nursing, University of Kentucky, Lexington. **This review was conducted without external funding. The authors declared no conflicts of interest.**

Computerized Therapy for Schizophrenia

A series of preliminary studies found a computer-based cognitive remediation therapy for schizophrenia to be both acceptable and easy to use.

Computerized Interactive Remediation of Cognition—a Training for Schizophrenia (CIRCuiTS) is a web-based cognitive remediation program that also offers alternate implementation offline.

It consists of a virtual village where users complete a total of 27 tasks, each with 12 levels of difficulty. Tasks are initially taught in an abstract manner, moving to more complex exercises involving multiple abilities, particularly executive function, in simulated situations such as work, shopping, or social life. The program can be individually tailored to patients' existing level of function, language, and cultural background. The program explicitly targets metacognition by encouraging participants to set goals and analyze their strengths and difficulties, working collaboratively with the therapist.

The CIRCuiTS program was evaluated in 4 successive studies in different groups: healthy volunteers who tried an early version; small numbers of patients from diverse ethnic backgrounds; patients treated by 3 therapists who used 2 intermediate versions; and 20 patients interviewed after they had received the latest version of CIRCuiTS as part of a controlled clinical trial. Nearly all participants reported that they liked using the computer, and that they enjoyed the program design and the experience of improving on tasks. Participants reported that CIRCuiTS improved their memory, and to a lesser extent, their attention and concentration, problem solving, and planning. Some said that the program was not enough to change their general thinking skills, but reported other benefits such as increased confidence. The majority had applied newly learned skills to their real lives, notably aids to memory and attention. Of the 20 clinical participants, 16 reported improvements between the start and end of individual sessions, such as greater motivation, confidence, and achievement. At the end of the entire program, they were glad to have more free time, felt a sense of achievement, and thought they would miss the therapist and the programs, but could cope with this emotion.

Because cognitive remediation is being recommended increasingly in treatment guidelines, there is a need to develop programs that would allow it to be used more widely. In contrast to CIRCuiTS, most cognitive remediation programs have not been designed for any specific diagnostic group. The CIRCuiTS program met predefined targets for acceptability, comprehensibility, and ease of use in the first 3 studies in clinicians, patients, and the public. In the fourth study, patients reported positive experiences, attempts to transfer the skills to daily life, no loss of self-esteem if they did not improve, and no adverse concerns over the end of therapy.

Reeder C, Pile V, Crawford P, Cella M, et al: The feasibility and acceptability to service users of CIRCuiTS, a computerized cognitive remediation therapy programme for schizophrenia. *Behavioural and Cognitive Psychotherapy* 2015; doi 10.1017/S1352465815000168. From King's College, London, U.K.; and other institutions. **Funded by the Medical Research Council; and the National Institute for Health Research. Two study authors disclosed financial relationships with commercial sources.**

Telemental Health Services

The delivery of mental health services via telecommunications systems is growing at a rapid pace, and given the reduced need for physical exams, imaging, and lab tests, telemental health will likely outpace the growth of electronic delivery in other areas of medicine, according to a review of the literature. Estimates suggest that up to 50% of all health care services will be conducted electronically by 2020.

There are currently 4 main types of telemental health services available: computerized CBT (cCBT); Internet-mediated CBT (iCBT); virtual reality exposure therapy (VRET); and mobile therapy (mTherapy). cCBT is the oldest, dating to the 1980s and predating the rise of the Internet. cCBT uses specifically designed software to allow patients to self-diagnose, personalize treatment goals, and use standardized therapy tools, with levels of clinician involvement ranging from none to minimal. iCBT is similar to cCBT, but because of the Internet connection, it can also offer real-time clinical contact, possibly including videoconferencing. Both forms of

electronically-assisted CBT have been studied in multiple clinical trials and meta-analyses, and both have been shown to be comparable to standard CBT for many outcomes. Real-time iCBT, (with or without videoconferencing) has been investigated in only a few studies, but appears to be similarly effective.

Another promising application of telemental technology is VRET, which uses tools such as headsets, motion sensors, and computer automated virtual environments to simulate real-life exposure situations. VRET has received less research than other electronic CBT, but efficacy data suggest it may be helpful in treating phobias, post-traumatic stress disorder, OCD, and substance use disorders. VRET has the advantages of additional control over the exposure and a sense of increased safety, but this technology is not yet widely available.

mTherapy may be favored over other telemental health tools by consumers, and there are >3000 mTherapy apps available for smartphones. These apps can help with diagnosis, self-monitoring, symptom tracking, and documentation; they may also help patients maintain adherence to traditional therapy by sending reminders to keep appointments and to do homework. To date, there have been only a handful of studies of the efficacy mobile apps. Other mTherapy interventions include text messaging and voice phone calls.

Telemental health services may expand patients' access to care; contain costs; improve efficiency; reduce the stigma of mental health care; and help patients with diagnosis-specific obstacles to treatment. Potential disadvantages include uncertain effects of technology on the therapeutic alliance, the lack of sufficient support, superficiality, and the need for specific computer skills. In addition, growth in telemental health services has outpaced scientific research, making it difficult to make recommendations about its efficacy in comparison to more standard interventions.

Aboujaoude E, Salame W, Naim L: Telemental health: a status update. *World Psychiatry* 2015:14 (June):223–230. From Stanford University School of Medicine, CA; and the Lebanese American University, Beirut, Lebanon. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

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

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

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Transcranial Stimulation for Geriatric Depression

Repetitive transcranial magnetic stimulation (rTMS) has lower antidepressant efficacy in the elderly, but according to a review, high-intensity regimens can increase the therapeutic response and should be made available to older patients.

Background: Most of the clinical trials of rTMS published to date have focused on younger adults. An early meta-analysis found a poorer response in elderly patients, but later analyses with a larger sample of studies failed to replicate this observation.

Methods: A systematic literature search was undertaken to identify all published studies, including randomized controlled trials, uncontrolled trials, and retrospective reviews, evaluating rTMS for geriatric depression. Only studies in which the population's mean age was >60 years, or in which efficacy was assessed in a subgroup of patients aged >60 years, were included. A second, broader search not limited by patient age was also conducted to identify treatment moderators in geriatric depression.

Results: A total of 4 randomized trials with sham controls were identified specifically in this age group. Two studies with small sample sizes found no benefit of rTMS. Two other larger studies found a substantial positive treatment effect. The 2 negative studies used a stimulation intensity that was fixed at or lower than the motor threshold. The 2 positive studies found that in resistant vascular depression, a higher dose (18,000 instead of 12,000 pulses) is more beneficial in older patients than younger patients. An additional 7 uncontrolled published trials conducted in patients aged >60 years were also identified. Response rates to rTMS in these trials ranged from about 20% to 60%. Four studies explicitly examined the effect of age on response, with 2 finding no effect of age and 2 finding a diminished response in elderly patients. Studies have consistently shown rTMS is highly tolerable and safe in this age group.

According to 4 published meta-analyses of direct comparisons of rTMS and ECT, which is known to be highly effective in elderly patients, ECT is superior to rTMS in older individuals.

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However, the 2 treatments may be equally effective when rTMS is given in an increased number of sessions or when the 2 treatments are compared in patients without psychotic symptoms. ECT results in a more rapid response than rTMS, but in 1 study the difference in efficacy decreased when the observation period was increased to 4 weeks.

Given the wide range of reported results in the elderly, several age-related factors may influence the efficacy of rTMS. Efficacy is inversely related to brain atrophy, but the treatment intensity may be adjusted to compensate. Efficacy is dose-related; almost all studies that showed efficacy in the elderly used a high number of rTMS pulses: 18,000. The possibly moderating effects of treatment resistance, psychosis, melancholic features, cognitive impairment, and medical comorbidities—all more prevalent in the elderly—require further investigation.

Discussion: Although this review suggests that older patients may benefit from rTMS, it may be premature to recommend the treatment for regular use in geriatric depression. It should not be considered a parallel option to ECT, as it is in younger adults. Rather, rTMS might be offered after an unsuccessful or poorly tolerated trial of ECT or when a rapid response is not crucial and cognitive side effects of ECT are likely.

Sabesan P, Lankappa S, Khalifa N, Krishnan V, et al: Transcranial magnetic stimulation for geriatric depression: promises and pitfalls. *World Journal of Psychiatry* 2015;5 (June 22):170–181. From Queen's Medical Center and the University of Nottingham, U.K. **Funded by the Nottinghamshire Healthcare National Health Services Trust. One study author disclosed a potential conflict of interest; the remaining 5 authors declared no competing interests.**

Psychiatric Disorders and Suicidal Ideation in College

Suicide prevention efforts in college students should be targeted toward identifying those with emotional volatility as well as those with depression, according to an analysis of data from a Web site designed to help college students screen themselves and others for mental-health conditions.

Background: College age, generally 18–24 years, is a stage during which many psychiatric disorders first emerge or peak. Research has shown that as many as one-third of college students have contemplated suicide at some point and that up to 6% of first-year students have current suicidal ideation. A Web-based survey was designed to characterize suicidal ideation and underlying psychiatric disorders in this at-risk population.

Methods: The anonymous Web-based assessment, the Self-Evaluator, was publicized mainly by college and university counseling centers and the schools' main Web sites and administered at http://www.ulifeline.org. Study participants were a nonrandom sample of >113,000 visitors from >1500 colleges and universities, mostly in the U.S. Initially, all patients were asked to check off a 10-item list of potential emotional areas of concern, including 2 symptoms of depression (dysphoric mood and anhedonia), emotional volatility (irritable, angry, or losing control), and thoughts of self-harm. Respondents were then guided through a branching pathway of questions based on the Composite International Diagnostic Interview. Diagnoses for 17 disorders were determined by symptom correspondence with DSM-IV-TR. In addition, participants were asked about 3 progressively more severe items assessing suicide risk. Participants could also complete an optional section with demographic information.

Results: One-fourth of respondents provided demographic information. Women made up three-fourths of this group, the median age was 20 years, and the typical respondent was a first-year student, single, and not currently employed.

The most prevalent disorder in the sample was depression (74%), followed by eating disorders (about 33%). About 20–33% of respondents qualified for each of the categories of social

phobia, panic disorder or agoraphobia, and post-traumatic stress disorder. The proportion with alcohol abuse was surprisingly low, about 3%, but 9% met criteria for alcohol dependence and 7% for non-alcohol substance use disorders.

Nearly half of respondents endorsed at least 1 of the 3 suicide items, which were thinking about death (36%), feeling like they wanted to die (34%), and thoughts of suicide (28%). In the 10 initial questions, about 40% of the participants endorsed thoughts about self-harm, about half endorsed emotional volatility, and nearly one-fourth endorsed both.

Contrary to the investigators' expectations, major depression was associated with one of the lowest frequencies of reported thoughts of self-harm of any of the psychiatric diagnoses (47%), and students with depressive symptoms were more likely to endorse emotional volatility (57%). Despite its status as the only disorder whose criteria include suicide, major depression fell below the median of disorders associated with responses to the 3 questions identifying suicide risk. Suicidal ideation was more strongly associated with physiological substance dependence, panic disorder with agoraphobia, bipolar disorder, substance abuse, PTSD, alcohol dependence, and obsessive-compulsive disorder.

Discussion: These results suggest it should not be assumed that suicide always begins with a depression-governed pre-suicidal syndrome that escalates in severity. It appears that in college students, suicide risk is more prevalent in other disorders. Risk assessment should not focus solely on a DSM diagnosis of depression; other psychiatric symptoms and emotional volatility should also be evaluated.

Tupler L, Hong J, Gibori R, Blitchington T, et al: Suicidal ideation and sex differences in relation to 18 major psychiatric disorders in college and university students: anonymous web-based assessment. *Journal of Nervous and Mental Disease* 2015;203 (April):269–278. From Duke University Medical Center, Durham, NC; and other institutions.
Funded by the Jed Foundation (a nonprofit suicide prevention organization), New York, NY; and other sources. The authors declared no conflicts of interest.

Eye Movement Therapy in Depression

In a preliminary controlled trial, eye movement desensitization and reprocessing (EMDR) therapy, widely regarded as effective in PTSD, had promising effects in patients with mild-to-moderate depression who had troubling memories of nontraumatic adverse life events.

Methods: Study subjects were 16 inpatients experiencing a mild-to-moderate depressive episode who consented to EMDR therapy and 16 age-, gender-, and diagnosis- (first-episode or recurrent) matched patients who did not receive EMDR. All patients received treatment as usual (TAU), which included individual psychodynamic psychotherapy, group therapy, and psychoeducation. EMDR therapy consisted of 60-minute sessions that focused on processing memories of adverse life events that did not meet the threshold for DSM-IV PTSD criterion A (experience or threat of death, serious injury, or loss of physical integrity; response of fear, helplessness, or horror). EMDR was administered once a week if a memory could be reprocessed in a single session; a second session was added if needed. Treatment efficacy was measured using the Symptom Checklist-90-Revised (SCL-90-R) depression subscale and the SCL-90-R global severity index.

Results: Patients received treatment for an average of about 6 weeks. The EMDR group received a mean of 4.6 sessions. Patients in both groups received, on average, about 6 individual and 7 group therapy sessions.

Patients who received EMDR therapy experienced significant relief of depression and global illness severity, with large effect sizes* compared with controls. (See table). Of the 16 patients who received EMDR therapy, 11 (68%) experienced full remission of depression, with Beck

Depression Inventory (BDI) scores <12. (Control subjects were not evaluated with the BDI.) Patients reported no adverse effects during reprocessing. Some had intense emotion during the session, which could be managed and reprocessed.

SCL-90-R Change from Baseline						
Outcome	EMDR + TAU		TAU only		Significance	Effect size
	Baseline	Post-treatment	Baseline	Post-treatment		
Depression subscale	20.9	6.9	23.7	19.6	p=0.047	1.02
Global severity index	1.12	0.42	1.28	1.16	p=0.015	1.18

Patients were contacted 12–16 months after the end of therapy. Of 11 in the EMDR group who provided follow-up data, 3 had experienced a relapse of depression, in contrast to 6 of 9 patients in the control group. The remaining 8 patients who received EMDR reported absence of depression at follow-up.

Discussion: A key assumption of EMDR therapy in depression is that some forms of depression are associated with disturbing memories of events. In this study, patients focused on events that precipitated their last or worst depressive episode. Typically they reprocessed memories of losses, separations, and humiliations. Another effective strategy was to work with negative beliefs and the memories on which they were founded.

Hase M, Balmaceda U, Hase A, Lehnung M, et al: Eye movement desensitization and reprocessing (EMDR) therapy in the treatment of depression: a matched pairs study in an inpatient setting. *Brain and Behavior* 2015; doi 10.1002/brb3.342. From the Diana Klinik, Bad Bevensen, Germany; and other institutions. **Source of funding not stated. Four study authors declared potential conflicts of interest, the remaining 3 authors declared no competing interests.**

***See Reference Guide.**

Illness Self-Management Programs

Available illness self-management (ISM) programs for adults with serious mental illness aim to increase self-directed recovery activities as a means of maximizing wellness and decreasing dependence on the service delivery system. The programs focus on controlling the disorder, maximizing overall health and wellness, and ameliorating the psychosocial sequelae of the illness. According to a review, the programs are diverse enough to offer a range of choices to fit the priorities of patients, clinicians, and administrators.

Five popular ISMs were chosen for review: Pathways to Recovery (PTR), The Recovery Workbook (TRW), Building Recovery of Individual Dreams and Goals through Education and Support (BRIDGES), Wellness and Recovery Action Planning (WRAP), and Illness Management and Recovery (IMR). The programs differ in structure and time commitment, ranging from self-help workbooks with optional group components to an intensive weekly individual or group program lasting 3–10 months, led by peer or professional facilitators. They use different methods of teaching, including self-help (PTR and TRW), peer leadership and mutual sharing (WRAP and BRIDGES), and role play (BRIDGES and IMR). Educational content of the programs also differs considerably, although all emphasize a holistic approach to pursuing recovery and encourage self-regulated learning through self-observation, self-assessment, and self-reactions.

Pathways to Recovery (PTR). This is a self-help workbook primarily intended for individual use that focuses on patients' strengths and promotes in-depth assessment of multiple

dimensions of recovery (e.g., housing, career development, financial management, sexuality). For each topic, strengths, resources, goal identification, and obstacles are assessed. The premise of PTR is that by reducing stress and allowing patients to experience success, the impact of mental illness will diminish. Efficacy of PTR is supported by a single clinical trial, showing improvement in widely used domains of recovery-oriented research.

The Recovery Workbook (TRW). This is a self-help workbook that provides structured activities for self-reflection directed at feelings, reactions, and goals in the context of identity development, while encouraging unstructured reflection in the form of journaling. TRW focuses on 4 areas affecting identity and recovery: impairment, dysfunction, disability, and disadvantage. The program provides minimal guidance and few concrete strategies for self-management, focusing instead on self-directed exploration and reflection. TRW efficacy is supported by a single clinical trial.

Building Recovery of Individual Dreams and Goals through Education and Support (BRIDGES). Typically delivered in a peer-led weekly meeting format over 8–10 weeks, BRIDGES is largely didactic and psychoeducational, with activities to build skills in problem-solving and interpersonal effectiveness. The program aims to increase knowledge about mental illness and recovery strategies in an environment where participants can educate and learn from one another. Participants engage in collaborative problem solving to both enhance skills and develop strategies to resolve barriers to recovery. BRIDGES also includes curriculum focused on the physiology of mental illness and the mechanisms of medications. BRIDGES has shown moderate treatment effectiveness in 2 studies.

Wellness and Recovery Action Planning (WRAP). In weekly group sessions conducted over 8 weeks, WRAP participants are helped to develop a comprehensive, goal-oriented action plan to promote, maintain, and reestablish wellness. Components of the program include: a proactive daily maintenance plan; contingency plans identifying ways to mitigate triggers and antecedents to decreasing wellness; a crisis plan; a post-crisis plan; and an advance directive to guide care in the event of crisis. Moderate effectiveness of WRAP was demonstrated in 2 large randomized controlled trials, both conducted by the creator of the program, along with numerous non-experimental studies.

Illness Management and Recovery (IMR). An intensive program delivered in weekly individual or group meetings over 3–10 months. IMR comprises instruction about mental illness as well as management and recovery strategies, and incorporates structured activities for skills building. Individual recovery goals are identified and broken down into manageable steps; progress toward goal attainment is monitored throughout participation. IMR balances collaboration and empowerment with didactic education and skills building. Program facilitators incorporate motivational interviewing strategies. IMR is highly structured, with educational handouts and worksheets guiding homework assignments. Skills enhancement activities include problem solving, decision making, social skills, and effective communication. IMR is the most widely researched ISM, evaluated in 16 studies that differed in design, rigor, attrition, faithfulness to the full program, and outcome measures. Although difficult to interpret, this evidence suggests IMR is moderately effective.

Discussion: All of these ISM programs promote wellness and recovery, but only IMR, BRIDGES, and TRW offer significant content on managing symptoms and controlling the disorder. While all of the programs have some evidence supporting their effectiveness in promoting recovery, the evidence is moderate at best. Selection among the specific programs should maximize the fit among consumer preference, clinician endorsement and skills, and agency culture and resources. PTR and TRW might be the best options for providers and

consumers seeking inexpensive programs with less structure and more self-guided reflection, with TRW providing a bit more structure via an optional manual for implementation in a group setting. WRAP offers an intermediate level of structure and may be the best fit for providers and consumers interested in developing comprehensive action plans. IMR requires a large consumer time commitment and organizational investment of staff time for training and implementation and might be a good fit for consumers desiring a comprehensive structured program with interaction with facilitators. BRIDGES is similar to IMR but shorter and, like WRAP, requires an agency investment in provider training.

Petros R, Solomon P: Reviewing illness self-management programs: a selection guide for consumers, practitioners, and administrators. *Psychiatric Services* 2015; doi 10.1176/appi.ps.201400355. From the University of Pennsylvania, Philadelphia. **Source of funding not stated. The authors declared no competing interests.**

ReferenceGuide

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

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PSYCHIATRY ALERTS NOS

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Mindfulness Therapy for Depression

In a preliminary study, mindfulness-based cognitive therapy (MBCT) showed promise as first-line, stand-alone treatment of major depressive disorder.

Background: MBCT is a group-based intervention that combines mindfulness meditation with cognitive behavioral concepts. It has been proven effective for depression relapse prevention following remission and as an augmentation strategy in resistant depression. There have been no controlled trials of MBCT monotherapy for acute depression.

Methods: A nonrandomized cohort of 23 patients who received MBCT was compared with a cohort of 20 patients who received treatment 2 years earlier in an open-label trial of sertraline (*Zoloft*) monotherapy. The MBCT cohort was selected to match the sertraline cohort in terms of gender, age, and depression severity. Participants in both cohorts were required to meet DSM-IV-TR criteria for major depressive disorder and to have a score of ≥17 on the 17-item Hamilton Rating Scale for Depression (HAM-D). No other pharmacotherapy or psychotherapy were permitted during the trials. MBCT was based on the manual for relapse-prevention but modified to address features of acute depression, such as agitation, decreased attention span, and executive impairment. Modifications consisted of reduced meditation time and increased time for mindful movement exercises. The MBCT program comprised 8 weekly group sessions (2 hours, 15 minutes each) with 8–12 participants. Daily meditation practice as homework was also recommended. Sertraline treatment also had a duration of 8 weeks. The HAM-D was the primary outcome measure in both studies.

Results: Both MBCT and sertraline were associated with significant improvement in depressive symptoms, with no difference between the groups in HAM-D improvement (11 and 8 points respectively). About 45% of each group experienced treatment response (i.e., ≥50% decline in the HAM-D score), and about 40% experienced remission (i.e., final HAM-D <8). MBCT was associated with a significantly larger improvement on the 16-item Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR).

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Potential mediators of response to MBCT were analyzed for use as early signals in future randomized studies. Improvement in depression was significantly associated with increased non-reactive thinking (p=0.017) and to a lesser degree, decreased isolation and increased decentering, observing, describing, and acting with awareness.

Discussion: MBCT appears to offer a promising alternative to medication for patients open to learning a useful skill set to manage their depression. It may have more lasting effects than antidepressants, as is suggested by its effects in relapse prevention. However, more rigorous studies with fewer limitations are warranted.

Eisendrath S, Gillung E, Delucchi K, Mathalon D, et al: A preliminary study: efficacy of mindfulness-based cognitive therapy versus sertraline as first-line treatments for major depressive disorder. *Mindfulness* 2015;6 (June):475–482. From the University of California, San Francisco; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

Magnetic Seizure Therapy for Depression

According to a systematic review of the limited available evidence, magnetic seizure therapy (MST) may be an effective treatment option for depressive episodes. Although less effective than electroconvulsive therapy (ECT), the relatively benign cognitive side-effect profile and the noninvasive nature appear to give MST a considerable advantage.

Methods: A systematic literature review identified all English-language publications of open-label or blinded studies of MST in unipolar or bipolar depression. A total of 8 studies met eligibility criteria and were included in the analysis. Clinical outcomes were reported in only 4 of the studies, with response defined as a ≥50% reduction in score on an established depression rating scale.

Results: Studies had sample sizes ranging from 7 to 20 MST-treated patients. Only 1 of the studies was a randomized, controlled, parallel-group trial. The majority of studies were conducted in patients with major depressive disorder, but a few included patients with bipolar depression. Two studies published before 2007 used 50-Hz equipment, and later studies used 100-Hz stimulation.

In an early comparative study, MST produced a smaller decrease in HAM-D score than ECT (-18 vs. -24 points, respectively) and was associated with a lower response rate (53%). However, the lower-intensity stimulation was used. Another comparative study in patients with resistant unipolar or bipolar depression showed similar efficacy with high-dose MST and ECT with response rates of 60% and 40%, respectively. Notably, the study used low-dose right unilateral ECT, a potentially less effective form than higher intensity treatment. In an open-label noncomparative study, MST was associated with response in 5 of 13 patients (38%), 2 of whom (15%) achieved remission. While ECT was not investigated in this study, the remission rate was substantially lower than that typically associated with ECT. In the final study, also open-label with no comparator, 4 of 10 patients who received treatment with MST (40%) met response criteria.

All 8 studies reported on the cognitive effects of MST. Generally, MST was associated with fewer subjective adverse cognitive effects, and recovery of orientation was faster with MST than with ECT. One study found MST to be superior to ECT on measures of attention, retrograde amnesia, and category fluency. Another study found disturbance in delayed recall on treatment days with ECT but not with MST. Several studies found seizure duration to be shorter with MST.

Discussion: The seizures induced by MST are more focused but also more superficial than those induced by ECT. Memory-related adverse effects may be less likely because medial

temporal lobe structures involved in memory are not stimulated. The clinical experience indicates MST is as effective as ECT in inducing seizures, but less effective in treating depression. Reported response rates have been between 40% and 60%, compared with 50–70% response rates for ECT in similar patient populations. The evidence base for MST is characterized by few studies, small sample sizes, weak study designs, and little standardization of treatment and assessment. Because stimulation parameters may affect efficacy, studies investigating higher-dose MST are currently underway.

Cretaz E, Brunoni A, Lafer B: Magnetic seizure therapy for unipolar and bipolar depression: a systematic review. *Neural Plasticity* 2015; doi 10.1155/2015/521398. From the University of Sao Paulo, Brazil. **Funded by the Brain and Behavior Research Foundation; and other sources. No study author declared relevant financial relationships with commercial sources.**

D-cycloserine, Antidepressants, and OCD

In a randomized trial of patients undergoing internet-based cognitive behavioral therapy (CBT) for obsessive-compulsive disorder, antidepressants may have blocked the effects of adjunctive D-cycloserine (*Seromycin*).[1]

Background: In patients with specific phobias, social anxiety disorder, and panic disorder, D-cycloserine has been shown to facilitate extinction learning when administered 1 hour before exposure.[2] D-cycloserine is a partial agonist at the NMDA receptor, and long-term exposure to antidepressants downregulates NMDA receptors and binding. However, the effects of antidepressants on D-cycloserine have not previously been studied.

Methods: Study participants (n=128) were patients with OCD and baseline scores of ≥16 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Patients were allowed to continue their background medication. All participants received 12 weeks of therapist-supported, Internet-based CBT using a protocol known to be effective in OCD and were randomized to receive either adjunctive placebo or 50 mg D-cycloserine. With their therapist's help, patients chose 5 exercises of exposure and response prevention (ERP). Study medication was to be taken 1 hour before each of the 5 ERP tasks. The primary outcome measure was the clinician-rated Y-BOCS, administered immediately post-treatment and at 3-month follow-up.

Results: In the primary analysis, D-cycloserine was not more effective than placebo. Patients in both treatment groups experienced significant improvements in Y-BOCS scores ($p<0.001$) from baseline with large effect sizes* in the post-treatment evaluation for both groups: 1.82 for D-cycloserine and 2.2 for placebo. These results were sustained at follow-up. There were also no significant differences between D-cycloserine and placebo on any secondary study outcomes, which included rates of response (about two-thirds of patients) and remission (about half), self-rated obsessive-compulsive symptoms, and measures of overall severity and function.

However, a post-hoc analysis showed that the effects of D-cycloserine were altered by concomitant antidepressant use. A separate analysis limited to patients taking D-cycloserine showed that the 21 patients also taking an antidepressant had significantly worse outcomes on the Y-BOCS and most secondary measures than those not taking antidepressants. At the study endpoint, patients receiving D-cycloserine with an antidepressant had a mean Y-BOCS score of 17, compared with 12 in patients not receiving an antidepressant ($p<0.05$). Y-BOCS scores at follow-up were 17 and 10 in the groups, respectively ($p<0.01$). Remission criteria were met by 24% of those taking antidepressants and 60% of those not taking them ($p=0.008$). In the placebo group, outcomes did not differ between those who did and did not receive antidepressants.

Discussion: Previous results with D-cycloserine have been mixed in patients with OCD, and the sample sizes have been too small to examine any possible interference from antidepressants.

The present results suggest that antidepressants may interact with D-cycloserine and block its effects on extinction learning, thus making D-cycloserine a reasonable augmentation agent only in antidepressant-free patients.

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

[1]Andersson E, Hedman E, Enander J, Djurfeldt D, et al: D-cycloserine vs placebo as adjunct to cognitive behavioral therapy for obsessive-compulsive disorder and interaction with antidepressants: a randomized clinical trial. *JAMA Psychiatry* 2015;72 (July):659–667. From Karolinska Institutet, Stockholm, Sweden; and other institutions. **Funded by the Swedish Research Council; and other sources. Three of the 13 study authors disclosed potentially relevant financial relationships.**

[2]Hofmann S, et al: Cognitive enhancers for the treatment of anxiety disorders. *Restorative Neurology and Neuroscience* 2013; doi 10.3233/RNN-139002. See *Psychiatry Alerts NOS* 2013;5 (May):26.

***See Reference Guide.**

N-acetylcysteine in Psychiatry

A derivative of the amino acid cysteine, N-acetylcysteine (NAC) is widely available over the counter as a supplement with antioxidant properties and is FDA-approved for treatment of acetaminophen overdose. It is known to be safe and well tolerated. NAC modulates many pathophysiological processes that may be involved in psychiatric disorders, including oxidative stress; neurogenesis and apoptosis; mitochondrial dysfunction; neuroinflammation; and dysregulation of glutamate and dopamine neurotransmitter systems. It may also have a role in long-term neuroadaptation and metaplasticity.

A comprehensive literature search identified published clinical studies of NAC for any psychiatric or neurologic disorder. The lack of standardized designs and outcomes precluded a meta-analysis of the 65 identified studies, but the authors ranked the evidence for each disorder on a scale from A (solid evidence) to D (limited, inconsistent, or inconclusive evidence). The grade was based on the quality of the studies, not necessarily the outcome. (See table.)

Psychiatric Condition	Evidence Grade	Results/Recommendations
Bipolar disorder	A	Mixed
Addictions*	B	Mixed/Not recommended
Autism	B	Mixed
Depressive disorder	B	Mixed
Impulse control—trichotillomania	B	Mixed
Schizophrenia	B	Mixed
Alzheimer's disease	C	Mixed
ADHD	C	None
Impulse Control—nail biting, skin picking	C	Mixed
OCD	C	Mixed
Anxiety	D	None

*Specific addictions (i.e., cannabis, cocaine, methamphetamine, nicotine, pathological gambling) were evaluated separately but are combined here because the evidence grade was the same for all.

Bipolar disorder was the only indication for which NAC studies received an A rating, based on 2 high-quality, randomized, controlled trials with medium-to-large sample sizes. However, results of the studies were inconsistent. In 1 placebo-controlled trial, NAC was associated with reduced severity of depressive symptoms but did not affect the frequency of or latency to new episodes of either depression or mania. A second study focused on depressive symptoms in 149 patients with bipolar disorder and a recent episode of moderate depression who received open-label NAC, added to usual treatment. Patients showed robust improvement in depressive symptoms, function, and quality of life. During the second, randomized, double-blind study phase, treatment was continued for 24 weeks with NAC or placebo. Again, latency to a mood episode was not affected. These results suggest that NAC may lessen the symptoms of bipolar episodes but not the frequency of cycling.

The evidence regarding NAC for several other disorders received a B rating, with only 1 randomized controlled trial or multiple studies of weaker design. There is limited evidence suggesting NAC may be effective for cocaine or cannabis addiction. For other addictions, including methamphetamine, nicotine, and pathologic gambling, the evidence is too preliminary to recommend for or against the use of NAC. In children with autism, NAC appears promising as a treatment for irritability. In the single, large (n=252), placebo-controlled trial of patients with major depressive disorder, NAC did not produce greater improvement in Montgomery-Asberg Depression Rating Scale (MADRS) scores, but effects on some secondary outcome measures were positive. Results of NAC for impulse control disorders have been inconsistent. Limited evidence suggests it may be effective in nail biting disorder; all studies that investigated NAC for skin picking suggested efficacy; and treatment was effective in adults, but not children, with trichotillomania. NAC also received a B rating for schizophrenia, with 1 large controlled trial showing significantly greater improvement in the NAC group on all qualitative and several quantitative measures. Another smaller study found that adding NAC to risperidone (*Risperdal*) improved PANSS negative and total scales. A case report also supports efficacy in treatment-resistant schizophrenia.

Grade C indications had mixed results, and there is little support of NAC use for them. Results in Alzheimer's disease were mixed. Recommendations cannot be made about the use of NAC for anxiety, as the only evidence is a single case report. The single study in ADHD included only patients with systemic lupus erythematosus and the results cannot be generalized to ADHD in the population as a whole.

Deepmala, Slattery J, Kumar N, Delhey L, et al: Clinical trials of N-acetylcysteine in psychiatry and neurology: a systematic review. *Neuroscience and Biobehavioral Reviews* 2015;55 (August):294–321. From Arkansas Children's Hospital, Little Rock; and other institutions. **The study was conducted without outside funding. Three authors declared potentially relevant financial relationships; the remaining 5 authors declared no conflicts of interest.**

Psychosocial Treatments for Bipolar Disorder

Evidence supports limited benefit of psychosocial interventions in patients with bipolar disorder. Individual interventions appear to target only specific aspects of the disorder in selected patient subgroups.

Methods: A literature search identified English-language, randomized, controlled trials of psychotherapy and psychosocial interventions in bipolar disorder (n=78). The studies described 7 different treatment approaches: cognitive behavioral therapy; psychoeducation; interpersonal and social rhythm therapy; family intervention; intensive psychosocial intervention; cognitive remediation and functional remediation; and mindfulness-based interventions. Efficacy of each approach was reviewed separately.

Results: In general, the psychosocial interventions are most effective in early stage of disease and in patients who are euthymic when recruited for study participation. Specific treatments appear to have differential effects, with neuroprotective strategies better during the early stages of disease and rehabilitation strategies preferable at later stages.

Psychoeducation in bipolar disorder concerns training patients in overall awareness of the disorder, treatment adherence, avoiding substance abuse, and early detection of new episodes. Review of 30 identified studies suggests it is the only approach with evidence of efficacy for relapse prevention. However, 6 months of group psychoeducation was only effective in preventing manic relapses and only in patients at the earliest stages of disease who were in remission at the start of therapy. Psychoeducation probably owes its efficacy to enhancing treatment adherence, promoting lifestyle regularity and healthy habits, and teaching early detection of prodromal signs.

Cognitive behavioral therapy (CBT) and **interpersonal social and rhythm therapy (IPSRT)** appear, from limited evidence (14 and 4 studies, respectively), to be useful in acute bipolar illness. CBT may be effective during the acute phase of depression, probably more so in patients in the early stages of illness; however, this group constitutes a minority of patients in usual clinical practice. IPSRT aims to correct circadian rhythm instability, improve medication adherence, and resolve interpersonal problems. There is equivocal evidence of its efficacy in improving both acute mania and depression, but it does not appear to be useful during the maintenance phase of bipolar disorder.

Mindfulness-based interventions, investigated in 8 studies of patients with bipolar disorder, involve education about the illness and relapse prevention, cognitive therapy, and training in mindfulness meditation to increase nonjudgmental awareness of the present moment. Some research suggests mindfulness therapy reduces anxiety in patients with bipolar disorder, but it may not improve the core features of the disorder.

Family-based interventions target the patient and his or her family/caregivers with elements of psychoeducation, communication enhancement, and problem-solving skills training. These programs, evaluated in 15 studies, were shown to have a beneficial effect on caregivers, but whether they help patients is unclear. Family interventions likely increase treatment adherence.

Less evidence exists for the efficacy of **intensive psychosocial interventions** (3 studies) and **cognitive remediation and functional remediation** (5 studies). Results of these studies are inconclusive or negative.

Miziou S, Tsitsipa E, Moysidou S, Karavelas V, et al: Psychosocial treatment and interventions for bipolar disorder: a systematic review. *Annals of General Psychiatry* 2015; doi 10.1186/s12991-015-0057-z. From Aristotle University of Thessaloniki, Greece. **Source of funding not stated. The authors declared no competing interests.**

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

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Brief Critical Time Intervention Reduces Rehospitalization

In patients at high risk of readmission following psychiatric hospital discharge, brief critical time intervention (BCTI) was associated with decreased early readmission rates.

Background: The transition in recent years from more common use of inpatient psychiatric care to mainly community-based treatment has resulted in shorter hospital stays. However, in part because the time after discharge poses so many challenges to the patient, up to 50% are re-admitted within 1 year. BCTI is a 3-month version of the evidence-based 9-month critical time intervention (CTI) model, which was originally developed to coordinate care for homeless patients with mental illness at times of transition.

Methods: This study examined the effects of BCTI on rates of readmission in consecutively discharged adults with serious mental illness, with or without co-occurring substance use disorders, who had ≥2 psychiatric admissions in the past 30 days. BCTI was integrated into an existing acute services coordination (ASC) intervention offered at a network of 6 community-based provider organizations for publicly funded patients. BCTI was offered in a 3-phase model: assessment of immediate needs and resources, ongoing connection to other community-based resources, and transition from ASC to community-based mental health services. BCTI enhanced ASC in multiple ways, including a focus on person-centered care, building autonomy, and linking with community-based food and housing resources. A similar group of patients who had been admitted about 1 year previously and received ASC without BCTI served as a comparison group. The primary outcome was early psychiatric hospital readmission (within 30 days of discharge).

Results: A total of 149 patients received BCTI, and 224 received ASC alone in the previous year. The BCTI cohort had a higher proportion of women, patients with substance-use disorders, and patients with anxiety or depression. Consequently, the primary analysis was adjusted for these factors. BCTI activities were completed at a high rate; 89% of patients met with their service coordinator before hospital discharge, and rates of treatment planning, needs assessment, and

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recovery planning ranged from 78% to 100%. The most commonly identified priorities were housing and income, treatment engagement, and substance-abuse treatment motivation.

Significantly fewer patients in the BCTI group than controls were readmitted within 30 days: 28% versus 47% (adjusted odds ratio,* 2.83; p<0.001). Rates of readmission between 31 and 180 days were also lower with BCTI, but the difference was not statistically significant.

Discussion: In this study, BCTI enhanced an existing service through the addition of more recovery-focused care, better monitoring of individual strengths and needs, and connection to community resources. Although use of a randomly selected control group would have been preferable, results of this study suggest that BCTI reduced readmissions in this high-risk population.

Shaffer S, Hutchison S, Ayers A, Goldberg R, et al: Brief critical time intervention to reduce psychiatric rehospitalization. *Psychiatric Services in Advance* 2015; doi 10.1176/appi.ps.201400362. From the Community Care Behavioral Health Organization, Pittsburgh, PA; and other institutions. **Funded by the Community Care Behavioral Health Organization. The authors disclosed no financial relationships with commercial sources.**

***See Reference Guide.**

ECT in OCD

According to a systematic review, there is no evidence to support the routine use of ECT in treating obsessive-compulsive disorder.

Background: About 10% of patients with OCD do not experience adequate response to the full range of evidence-based treatments. A trial of ECT has been discussed as an additional step, before trying a more invasive procedure, but the strategy has not been systematically evaluated.

Methods: A comprehensive literature search identified all types of studies of ECT in OCD. Studies were included regardless of whether patients had comorbid psychiatric disorders and whether other forms of treatment were started or maintained with ECT. The search identified no randomized trials, 1 quasi-randomized study, 1 case-control study, 1 cohort study, 22 case series, and 25 single-case reports. The primary outcome measure was each study authors' report of a significant reduction in OCD severity.

Results: In the quasi-randomized trial, participants were allocated to ECT (n=17) or antidepressants (SRIs or "cyclic"; n=49). Clinical Global Impression–Improvement ratings showed marked improvement in 60% of each treatment group. Baseline and final scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) were obtained but not reported, which raises the possibility of selective reporting of outcomes. In addition, methodological details were limited.

In the only other study that included a comparison group, treatment for the 43 patients was heterogeneous and flexible, consisting of various oral and intravenous (IV) antidepressants with or without ECT. Treatment arms were identified retrospectively, with 2 of the 4 groups (n=19) receiving ECT. "Cure" was reported in about two-thirds of the 2 ECT groups and similar proportions of the non-ECT groups, but patients with more severe illness were more likely to receive ECT and IV antidepressants.

The case series and case reports included a total of 279 patients. Positive responses were reported in 60% of the patients; however, Y-BOCS scores were available for only 7 patients (2.5%). Response rates were similar in cases published before and after the widespread availability of SRIs and cognitive-behavioral therapy, which suggests that the inclusion of patients who would now qualify as non-treatment-resistant was similar in both eras. Treatment-resistant OCD was the indication for ECT identified in the overwhelming majority of cases, but previous

exposure to an SRI or CBT was described in less than half of patients and there was little information on the adequacy of prior treatment. Patients who experienced response to ECT appeared to be less likely to have received previous treatment with adequate doses of an SRI prescribed for a sufficient time and were less often prescribed CBT. In the few reports that included follow-up data, maintenance of initial improvement was lost in about one-third of patients.

Fontenelle L, Coutinho E, Lins-Martins N, Fitzgerald P, et al: Electroconvulsive therapy for obsessive-compulsive disorder: a systematic review. *Journal of Clinical Psychiatry* 2015;76 (July):949–957. From the Federal University of Rio de Janeiro, Brazil; and other institutions. **Funded by the Fundacao de Amparo a Pesquisa do Estado de Rio de Janeiro; and other sources. One study author disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

Nonconvulsive ECT for Resistant Depression

In an open-label proof-of-concept study, nonconvulsive electrotherapy (NET), which uses the standard techniques of ECT but at a dose below the seizure threshold, was effective in a small group of patients with treatment-resistant depression.

Methods: Open-label NET was administered to 13 outpatients (mean age, 40 years) with unipolar or bipolar major depressive disorder, a baseline score of ≥16 on the 17-item Hamilton Rating Scale for Depression (HAM-D) despite ongoing medication, and refusal of ECT due to concern about adverse effects. All patients received a full pre-ECT clinical assessment. The ECT device was modified by the manufacturer to deliver doses below the standard machine-set minimum. Patients were administered NET under standard ECT anesthesia. They received brief-pulse bifrontal electrical stimulation 3 times per week at half the standard calculated ECT dose, later reduced to one-eighth the standard ECT dose after seizures were induced in the first 3 patients. Response was defined as a ≥50% decrease from baseline in HAM-D score, and remission as a score of <8. Patients were withdrawn from NET if they did not demonstrate a ≥25% improvement after 4 treatments or a ≥50% improvement after 8 treatments. Those who met minimum improvement requirements were continued in the study until they met remission criteria or underwent 3 consecutive treatments with no further improvement.

Results: The duration of the current depressive episode in the study patients averaged 2 years, and they had undergone a mean of 4.5 medication trials. Of 13 enrolled patients, 2 experienced a seizure with their first treatment and were not included in the analysis. Data from the first 4 sessions for another patient, who had a seizure during the fifth treatment, were included. Patients received an average of 7 NET treatments at 2–3 joules.

Overall, the mean HAM-D score decreased from 20 at baseline to 9 after completion of NET ($p=0.001$). A significant difference was noted by the fourth treatment. Three patients were withdrawn from NET for lack of response after the fourth session. Eight patients met response criteria, including 6 who achieved remission of depression. The average time to reorientation after treatment was 6 minutes. Mean post-treatment scores on a measure of memory were nearly identical to pretreatment scores.

Discussion: This finding challenges the widely held belief that a generalized seizure is necessary for the antidepressant effects of electrical brain stimulation. The authors suggest that NET may owe its efficacy to bifrontal electrode placement, which targets brain regions that are critically involved in depression.

Regenold W, Noorani R, Piez D, Patel P: Nonconvulsive electrotherapy for treatment resistant unipolar and bipolar major depressive disorder: a proof-of-concept trial. *Brain Stimulation* 2015; doi 10.1016/j.brs.2015.06.011. From the University of Maryland, Baltimore. **Funded by the National Alliance for Research on Schizophrenia and Depression. The study authors declared no conflicts of interest.**

Impaired Glucose Metabolism and Suicidal Behavior

In a cohort of middle-aged patients with depression, suicidal thoughts and behavior were associated with higher plasma glucose levels, probably the result of insulin resistance. High lipid levels were also associated with suicidality.

Methods: This registry-based study, conducted in Finland, included 448 patients aged ≥35 years who were referred or self-referred for primary-care management of a first depressive episode in 2008–2009. Study subjects were required to have a Beck Depression Inventory (BDI) score of ≥10 upon referral. Suicidal behavior was defined as suicidal ideation during the past month or a lifetime history of suicide attempt. Fasting glucose and lipid levels were measured at baseline, followed by a 2-hour oral glucose tolerance test.

Results: Nearly half of the patients (49%) were experiencing suicidal thoughts, and 72 (16%) had a past suicide attempt. Study participants with suicidal behavior also had more severe depression and a higher prevalence of alcohol use disorder. Patients with suicidal behavior had higher blood glucose levels when fasting (109 vs. 103 mg/dL; p=0.013) and after 2-hour glucose challenge (121 vs. 105 mg/dL; p=0.0013) than those without suicidal behavior. The 2 glucose measurements each had a highly significant linear association with the presence of suicidal behavior. Compared with the lowest tertile, patients in the highest tertile of fasting glucose had an elevated risk of suicidality (odds ratio,* 2.18); for 2-hour glucose, the odds ratio for the highest versus lowest tertile was 1.99.

Baseline and 2-hour insulin levels did not differ as a function of suicidal behavior. Patients with suicidal behavior had higher scores on the Quantitative Insulin Sensitivity Check Index (QUICKI), a measure of insulin resistance; higher total cholesterol, LDL cholesterol, and triglycerides; and higher scores on the BDI.

Discussion: It is likely that elevated glucose in suicidal patients was related to insulin resistance, rather than insufficient insulin secretion. Reduced serotonin levels have been associated with increased weight and waist circumference, elevated glucose, and insulin resistance. Impaired glucose tolerance may be linked to suicide via cytokine-mediated inflammation, resulting in depletion of tryptophan and emerging serotonergic hypofunction, depression, and impulsivity.

Koponen H, Kautiainen H, Leppanen E, Mantyselka P, et al: Association between suicidal behavior and impaired glucose metabolism in depressive disorders. *BMC Psychiatry* 2015; doi 10.1186/s12888-015-0567-x. From the University of Helsinki, Finland; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

***See Reference Guide.**

Security of Electronic Mental-Health Data

Use of electronic communication continues to increase in mental-health settings. In order to avoid exposure to HIPAA violations, licensing sanctions, and civil lawsuits, clinicians must maintain rigorous practices to maintain privacy and security.

Networks that are hard wired are generally safe from hackers as long as the consumer is using a firewall, which is generally built into the router or available as an option on the computer's operating system. Wireless networks are vulnerable, whether in the patient's home or in hospitals and clinics that offer access to staff and patients. These networks should be password-protected using WPA encryption, rather than less secure WEP encryption. Users should communicate only using encrypted websites—i.e., those using the "https" prefix. Https is offered as an option by most major email providers, such as Gmail, Yahoo,

and Hotmail. With a free program called HTTPS Everywhere, users can automatically activate https encryption. A more secure option is to install a virtual private network (VPN) on public computers.

Videoconferencing, increasingly used to deliver mental-health treatment, should not occur via free services like Skype or FaceTime. Security can be increased by using a VPN, high-end videoconferencing hardware, or security-enhancing add-ons to the free services (e.g., Doxy.me).

Cell phone instant messages can be intercepted by hackers or viewed by anyone if a phone is lost, stolen, or left unattended. Clinicians should turn on the password protection on their mobile devices and instruct patients to do the same. Providers should also avoid using Short Message Service (SMS) or instant messaging, instead opting for encrypted self-destructing messages. Wickr is a free application for encrypting messages. If the patient needs a return phone call or text outside of office hours, calls/texts can be made from a cell phone without providing the patient with the clinician's private number using the Burner app.

Computers used in the office or clinic should also be kept secure from hacking. Windows and Apple computers are configured to provide automatic security updates, but all computers should be scanned weekly with antivirus software, also available from Microsoft or Apple. Computers that contain patient data or communications should be encrypted, as should the contents of flash/USB drives. Computers should have a firmware (Apple) or BIOS (Windows) password. Computers should be disposed of properly, using a secure erase or physically destroying the hard drive, rather than merely deleting data. For data backups, cloud storage is generally secure and preferable to copying data locally. Clinicians should also periodically review the privacy settings on their social network sites.

Privacy is a crucial aspect of mental-health care for which providers are responsible. Common privacy and security measures may not be adequate to comply with HIPAA requirements for communication and record keeping, and clinicians should carefully monitor the security of their technology use.

Elhai J, Frueh B: Security of electronic mental health communication and record-keeping in the digital age. *Journal of Clinical Psychiatry* 2015; doi 10.4088/JCP.14r09506. From the University of Toledo, OH; and other institutions. **This article was not funded. The study authors declared no conflicts of interest.**

Rating Scales for Antipsychotic-Induced Adverse Effects

The selection of antipsychotic adverse-effect rating scales for use in research is driven by psychometric properties, but in clinical practice, completeness of symptom coverage and ease of use may be more important. According to results of a systematic review, adverse effects of antipsychotic medication in chronically ill patients may be best assessed using multi-domain patient-completed questionnaires.

Methods: English- and Dutch-language publications describing rating scales for antipsychotic adverse effects were identified by literature search. Psychometric characteristics of the scales were compared in terms of reliability and validity using various measures of correlation.

Results: The search identified 440 studies, of which 46 described the psychometric properties of a scale and 394 described clinical use of a scale. A total of 14 of the evaluated scales were for multi-domain adverse effects, 29 of the scales were limited to extrapyramidal effects, 7 measured sexual dysfunction, and 3 assessed other single-domain adverse effects. The most frequently used multi-domain scales were the Udvalg for Kliniske Undersogelser Side Effects Rating Scale for Clinicians (UKU-SERS-Clin) and the Liverpool University Side Effect Rating Scale (LUNSERS). The most commonly used extrapyramidal-symptom scales were the Simpson-Angus Scale (SAS), the Abnormal Involuntary Movements Scale (AIMS), and

the Barnes Akathisia Rating Scale (BARS). The scales for sexual and other adverse effects were used infrequently.

The multidimensional scales with the best psychometric characteristics were the UKU-SERS Patient (Pat) and Clinician versions, the LUNSERS, and the Glasgow Antipsychotic Side-effect Scale (GASS). Each of these has different advantages—e.g., the GASS takes only 5 minutes to complete and grades severity and frequency of adverse effects; the LUNSERS and the UKU-SERS are more comprehensive; and the LUNSERS has "red herring" items to detect over-reporting of symptoms. Of the extrapyramidal-symptom scales, the ones with the best psychometric performance were the SAS, the Drug-Induced Extrapyramidal Symptom Scale, and the Maryland Psychiatric Research Center Scale. The Antipsychotics and Sexual Functioning Questionnaire and the Nagoya Sexual Functioning Questionnaire had the best psychometric characteristics for measuring sexual side effects.

Discussion: It is essential to assess medication adverse effects in clinical practice, particularly in patients receiving antipsychotics. Multi-domain rating scales are preferable to single-symptom scales because they can capture effects that would otherwise be missed if patients are not directly questioned about them or if they do not recognize a problem as a medication effect. Patients who are clinically stable can complete a multidimensional scale—e.g., the UKU-SERS-Pat, LUNSERS, or GASS—relatively quickly in the waiting room before their appointment. Their responses can facilitate a discussion of adverse effects and tolerability.

van Strien A, Keijsers C, Derijks H, van Marum R: Rating scales to measure side effects of antipsychotic medication: a systematic review. *Journal of Psychopharmacology* 2015; doi 10.1177/0269881115593893. From Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands. **This research was not funded. The authors declared no potential conflicts of interest.**

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

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CBT for Seasonal Depression

Preliminary results from a randomized trial indicate that an adapted form of cognitive behavioral therapy was as effective as light therapy, the recommended treatment, for seasonal affective disorder (SAD).

Methods: Study subjects (n=177), recruited in Vermont during the fall or early winter, met DSM-IV-TR criteria for recurrent major depressive disorder with a seasonal pattern as well as Structured Interview Guide for the Hamilton Rating Scale for Depression-Seasonal Affective Disorder Version (SIGH-SAD) criteria for SAD. Participants were randomly assigned to 6 weeks of treatment with either light therapy, monitored by therapists with dosage adjustment as needed, or to CBT specifically adapted for treatment of SAD (CBT-SAD). The CBT protocol was administered in a small-group format (4–8 patients) over 6 weeks and focused on behavioral activation and cognitive restructuring to improve coping with winter; the treatment concluded with a personalized relapse prevention plan. CBT-SAD was delivered by PhD-level community therapists with experience in CBT and clinical psychology graduate student co-therapists. The primary aim of this continuing study is to compare rates of SAD relapse after 2 years. The present interim analysis compared acute outcomes, evaluated by blinded raters, after treatment completion.

Results: At baseline, about one-fourth of the study patients had comorbid psychopathology or were taking an antidepressant. One patient did not complete light therapy, and 13 patients withdrew from SAD-CBT prematurely. Harmful or unintended effects of treatment were not reported in either group.

Both treatments were associated with large improvements in depression severity. Mean SIGH-SAD scores decreased from about 28 at baseline to 12, with no difference between the 2 treatments. Similar large improvements were observed on secondary outcome measures including the Hamilton Rating Scale for Depression, the atypical symptoms subscale of the SIGH-SAD, and the Beck Depression Inventory, again with no difference between treatments.

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Remission, defined using various cutoffs on the 3 depression measurement scales, was achieved by about half of patients in each group.

Discussion: Daily light therapy, beginning at symptom onset and continuing until remission in the spring or summer, is currently the recommended treatment for SAD. However, because nearly half of treated patients do not achieve remission, additional treatment options are needed. The present results indicate that CBT-SAD is at least as effective as light therapy, and the authors suggest it should be considered a viable alternative to light therapy.

Rohan K, Mahon J, Evans M, Ho S-Y, et al: Randomized trial of cognitive-behavioral therapy versus light therapy for seasonal affective disorder: acute outcomes. *American Journal of Psychiatry* 2014;172 (September):862–869. From the University of Vermont, Burlington; and other institutions. **Funded by the NIMH. One study author disclosed financial relationships relevant to the study; the remaining authors declared no competing interests.**

Cardiac Risk Factors in Schizophrenia

In a study of patients with schizophrenia, risk of sudden cardiac death was associated with physically aggressive behavior, in addition to physical illness and treatment with an antipsychotic drug.

Methods: For the study, data were collected for consecutive admissions for schizophrenia at a single treatment center in Taiwan over a 23-year period. Of >8000 patients admitted, sudden cardiac death occurred in 64. These patients were each matched with ≤2 controls who had a similar comprehensive level of information available in the chart, resulting in 53 cases with ≥1 match. Standardized mortality ratios (SMR)* were calculated based on the general population.

Results: Patients with schizophrenia had an SMR of 4.5 for all-cause mortality. The SMR for sudden cardiac death was also 4.5, with an incidence of 81.4 deaths per 100,000 person-years. Patients who experienced sudden cardiac death had a mean age of 46 years at their index (first) admission. Sudden cardiac death occurred an average of 5 years after the index admission; no patient experienced sudden cardiac death during their index admission. Of note, the index admission was the only admission for 43 of 53 case patients but for only half of controls. The specific cause of sudden cardiac death was coronary artery disease in 18 patients, arrhythmia in 12, congestive heart failure in 11, and other or poorly defined pathology in the rest.

There were no important demographic predictors of sudden cardiac death. However, several clinical features were statistically significant risk factors. (See table.) Aggressive behavior at both the index visit and the most recent visit was predictive, while the association with the other factors was significant only for 1 visit, as indicated. Although physical illness at the index visit was strongly predictive of sudden cardiac death, risk was not associated with diabetes, cardiovascular disease, metabolic profiles, or laboratory values. A multivariate analysis confirmed that at the index admission, physical aggression and physical disease predicted sudden cardiac death. Among data available at the most recent visit, sudden cardiac death was predicted by aggressive behavior, use of a first-generation antipsychotic, and electrocardiogram abnormalities.

Clinical characteristics predictive of sudden cardiac death in schizophrenia, based on index or latest admission

Risk factor (admission)	Prevalence in cases (n=53)	Prevalence in controls (n=103)	Unadjusted risk ratio*	Significance
Aggressive behavior (index)	32%	13%	3.51	p=0.007
Physical disease (index)	62%	37%	2.85	p=0.004
Aggressive behavior (latest)	34%	12%	4.38	p=0.002
Abnormal ECG (latest)	17%	4%	4.39	p=0.033
First-generation antipsychotic only (latest)	77%	57%	3.78	p=0.006

Discussion: The association of sudden cardiac death with physical aggression should be interpreted with caution because of the low number of patients with aggression. However, the association seems reasonable as aggressive patients may receive higher antipsychotic doses or multiple agents, leading to higher drug-related cardiovascular risk. They may also be likely to form a poorer therapeutic alliance, leading to suboptimal outcomes.

Hou P-Y, Hung G, Jhong J-R, Tsai S-Y, et al: Risk factors for sudden cardiac death among patients with schizophrenia. *Schizophrenia Research* 2015; doi 10.1016/j.schres.2015.07.015. From Taipei City Hospital, Taiwan; and other institutions. **Funded by the National Science Council, Taiwan; and Taipei City Hospital. The authors declared no competing interests.**

***See Reference Guide.**

Suicide Risk After Nonfatal Self-Harm

Risk of suicide is particularly high during the year after nonfatal deliberate self-injury in patients with bipolar disorder, psychosis, or depression, according to results of a cohort study. Aftercare of the self-harm episode should focus on treatment of the mental disorder present at the time of the episode.

Methods: Data from a Swedish registry that covers all inpatient health care were analyzed to determine risk of completed suicide after a self-harm event. The study cohort included all Swedish residents, aged >10 years, who had been hospitalized in 2000–2005 for deliberate self-harm or self-harm with undetermined intent. It was not possible to determine whether these episodes were suicide attempts. Also evaluated were the method of self-harm and whether the patient received a psychiatric diagnosis during the self-harm admission or soon afterward. Suicides in the years following the self-harm episodes were identified in Sweden's national Cause of Death register.

Results: The cohort consisted of >34,000 persons—about 14,000 men and 20,000 women. A total of 1182 suicides occurred after the index hospitalization. Compared with patients without mental illness, suicide risk was elevated for all categories of psychiatric diagnosis. The suicide rate was highest in patients with bipolar disorder (adjusted hazard ratios [HR],* 6.3 in men and 5.8 in women). Risks were nearly as high in men and women with nonorganic psychotic disorder (HR, 5.1 and 4.6, respectively) or moderate-to-severe depression (HR, 4.8 in both genders) and in women with personality disorder (HR, 4.5). Risk was also elevated in both women (HR, 2.8) and men (HR, 4.6) with substance use disorder coexisting with and any affective disorder.

Suicide risk also differed according to the method of self-harm. Compared with self-poisoning, the most common method and the reference category, risks were elevated for most other methods of self-injury and were highest for hanging, strangling, or suffocation, followed by drowning, using firearms/explosions, and jumping from a height. When information about risks was combined, the highest risks were for patients with bipolar disorder who used a self-injury method other than poisoning (HR, 12.9 in men and 15.8 in women). A total of 20% of all patients with bipolar disorder who used a self-injury method later committed suicide.

Discussion: This study was conducted in part to determine whether suicide risk prediction had been affected by recent changes, such as greater availability of mental health treatment and decreases in the suicide rate. Risk patterns do not appear to have changed much from previous decades, and although psychiatric treatment after nonfatal deliberate self-harm may have improved, the prognosis is still poor in patients with a coexisting severe mental disorder.

Runeson B, Haglund A, Lichtenstein P, Tidemalm D: Suicide risk after nonfatal self-harm: a national cohort study, 2000-2008. *Journal of Clinical Psychiatry* 2015; doi 10.4088/JCP.14m09453. From the Karolinska Institute, Stockholm, Sweden. **Funded by the Stockholm County Council; and other sources. The authors declared no conflicts of interest.**

***See Reference Guide.**

Group Therapy for Negative Symptoms

In a small pilot study, promising results were observed for a group therapy to reduce anhedonia and apathy in schizophrenia by challenging defeatist thinking.

Background: The negative symptoms associated with diminished capacity to experience—anhedonia, asociality, avolition—are linked to a poorer prognosis in patients with schizophrenia. The Positive Emotions Program for Schizophrenia (PEPS) is a new intervention designed to improve apathy and anhedonia by increasing participants' cognitive control of positive emotions, including the pleasurable anticipation and recall of positive experiences.

Methods: Study participants were 37 adults, aged 18–65 years, with schizophrenia or schizoaffective disorder and a score of ≥2 on the Scale for the Assessment of Negative Symptoms (SANS) Anhedonia scale. All but 1 patient were taking antipsychotic medication, and 14 were also receiving antidepressants. The intervention consisted of 8 group sessions (1 hour each), in which participants were guided through a routine of cognitive restructuring exercises and review of homework assignments. The program taught the skills of savoring a present or past pleasant experience, behaviorally expressing positive emotions, making the most of positive moments, and anticipating pleasant experiences. Change from baseline in the SANS Apathy and Anhedonia scores was the main efficacy endpoint. Patients were also assessed at baseline and after treatment with the Calgary Depression Scale for Schizophrenia (CDSS) and the 24-item Savoring Belief Inventory.

Results: PEPS was associated with a moderate improvement in the Avolition-Apathy scale of the SANS (effect size,* 0.57; p=0.001) and in the Anhedonia-Asociality scale (effect size, 0.50; p=0.001). The change in CDSS scores showed a large improvement in depression (effect size, 0.91). Treatment did not significantly affect SANS scores for Affective flattening, Alogia, and Attention. Change from baseline in the SANS total score and the Savoring Belief Inventory also did not reach statistical significance.

To separate the effects on anhedonia from depression, independent analyses were conducted in the 17 patients with concurrent depression (CDSS score >6) and the 14 patients without depression. Patients with depression showed the largest improvement in avolition and apathy. By end of study, only 9 (53%) continued to meet depression criteria.

Discussion: As suggested by previous literature, schizophrenia is associated with diminished capacity to anticipate or savor anticipatory pleasure rather than in-the-moment pleasure. Affective flattening and alogia were unaffected by treatment, which suggests the effect of PEPS is specific to anhedonia and apathy. Patients' acceptance of this program is evidenced by the high rate of treatment completion (31 of 37 patients).

Favrod J, Nguyen A, Fankhauser C, Ismailaj A, et al: Positive Emotions Program for Schizophrenia (PEPS): a pilot intervention to reduce anhedonia and apathy. *BMC Psychiatry* 2015; doi 10.1186/s12888-015-0610-y. From the University of Applied Sciences and Arts of Western Switzerland and the University Hospital Center, Lausanne, Switzerland. **Funded by a private donor. The authors declared no competing interests.**

***See Reference Guide.**

Botox Injection for Depression

Botulinum toxin injections to the forehead are a promising treatment for depression, according to a meta-analysis of 3 placebo-controlled trials.

Methods: A literature search identified 3 published studies of botulinum toxin injections for the treatment of depression. All 3 trials were investigator-initiated, non-industry-funded studies, each conducted by 1 of the present meta-analysis authors. In the studies, patients

with unipolar major depressive disorder, had been randomly assigned to a single session of onabotulinumtoxinA (*Botox*) or saline placebo injection at 5 points in the glabellar frown lines. Depression symptoms were assessed 6 weeks later using the clinician-rated Hamilton Rating Scale for Depression (HAM-D) in 2 studies and the Montgomery-Asberg Depression Rating Scale (MADRS) in 1, as well as the patient-rated Beck Depression Inventory (BDI) in all 3. The primary efficacy endpoint was the percent change from baseline in the clinician-rated scales. Response was defined as a ≥50% decrease in depression rating scale score, and remission as a score of ≤7 on the HAM-D, ≤10 on the MADRS, and ≤9 on the BDI.

Results: In total, 59 patients received injections with botulinum toxin and 75 received placebo. Patients had a mean age of 49 years, and about 90% were women. The average duration of the current depressive episode was >2 years. Depression was recurrent in 85% of the total group and at least moderately severe in about 90%; two-thirds of patients were receiving antidepressant medications.

Botulinum toxin was superior to placebo for all efficacy outcomes. (See table.) Response rates did not differ according to baseline antidepressant use.

Clinician- and self-rated depression outcomes 6 weeks after injection of botulinum toxin or placebo

	Botulinum Toxin (n=59)	Placebo (n=75)	Odds Ratio*	Number Needed to Treat
Clinician-Rated Scales				
% Reduction	46%	15%	—	—
Response (%)	54%	11%	11.1	2.3
Remission (%)	31%	7%	7.3	4.2
Self-Rated BDI				
% Change from baseline	47%	16%	—	—
Response (%)	53%	8%	11.1	2.2
Remission (%)	41%	8%	15.7	2.9

Discussion: Positive effects of botulinum toxin injections in depression may be explained by the facial feedback hypothesis: paralysis of the injected frown muscles interrupts a feedback loop between negative facial expression and negative emotion. This hypothesis has been substantiated in several experimental studies, but it is also possible that cosmetic improvement and social feedback may explain some of the response, and direct drug effects on sensory neurons or even transport to the CNS may have a role in relieving depression. An important limitation of 2 of the studies is the difficulty of preserving participant blinding when the cosmetic effects of active treatment are obvious. Also, there were too few male subjects included in these studies to determine efficacy in men.

Study Rating*—14 (78%): This study met most criteria for a systematic review/meta-analysis; however, individual study quality was not assessed and the source of meta-analysis funding was not stated.

Magid M, Finzi E, Kruger T, Robertson H, et al: Treating depression with botulinum toxin: a pooled analysis of randomized controlled trials. *Pharmacopsychiatry* 2015;48:205–210. From the University of Texas at Austin; and other institutions. The individual trials were funded by the Gottfried & Julia Bangerter-Rhyner-Stiftung, Bern, Switzerland; the Brain & Behavior Research Foundation, NY; and the Chevy Chase Cosmetic Center, MD. **Source of meta-analysis funding not stated. Five study authors declared financial relationships with commercial sources; the remaining 4 authors declared no competing interests.** See related story in *Psychiatry Alerts* NOS 2014;6 (May):27.

***See Reference Guide.**

Psychotropic Nomenclature

There are 5 major drug classes in the traditional psychopharmacology nomenclature created in the 1960's: antidepressants; antipsychotics; mood stabilizers; sedative-anxiolytics; and stimulants. In light of the upsurge in neuroscientific research and an increased focus on biological mechanisms of treatments, a need for new nomenclature has been suggested.

A nomenclature task force—composed of members of the European College of Neuropsychopharmacology, the American College of Neuropharmacology, the Collegium Internationale Neuropsychopharmacologicum, and the Asian College of Neuropsychopharmacology—proposed a fundamental change in the way that psychotropic drugs are named. Their proposed nomenclature is based on the biological mechanisms of drugs, rather than on the indication for which they were developed.

Altering the nomenclature could facilitate patient understanding and eliminate misconceptions about medications based on the old categorization. For example, a patient with unipolar depression may not understand why they are receiving a prescription for an antipsychotic, such as quetiapine (*Seroquel*), which has antidepressant properties, when they are not experiencing psychosis. Under the newly proposed nomenclature, quetiapine would no longer be categorized in relation to a specific disorder, but rather would be described in terms of its biological mechanism, thereby reducing patient confusion. In addition, a discussion of a drug's mechanism of action, based on the naming convention, could also facilitate patient's understanding of the biological underpinnings of their disorder, as well as potential adverse effects of their prescribed medications.

Ghaemi S: A new nomenclature for psychotropic drugs. *Journal of Clinical Psychopharmacology* 2015;35 (August): 428–433. From Tufts Medical Center, Boston, MA. The author disclosed receiving research grants from several pharmaceutical sources, but declared he holds no equity position in a pharmaceutical corporation.

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

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

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.

Standardized Mortality Ratio: The ratio of observed deaths in a study group to expected deaths in the general population.

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

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Deep Transcranial Stimulation for Depression

High-frequency deep transcranial magnetic stimulation (DTMS) is effective and acceptable to patients as acute treatment of major depression, according to results of a meta-analysis.

Background: In contrast to repetitive transcranial magnetic stimulation (rTMS), DTMS uses an "H-coil" system to provide focused stimulation of deeper reward-mediating brain regions while reducing the activation of cortical areas. It has been suggested that deeper stimulation might produce greater antidepressant effects, although no head-to-head comparisons of rTMS and DTMS have been conducted.

Methods: A comprehensive literature search identified all studies of DTMS published in peer-reviewed journals (or in press) through 2015. To be included, studies were required to have treated ≥5 patients, administered DTMS with H-coils, measured treatment outcome with a standardized depression rating scale, and reported adequate data to calculate effect sizes.* Response was defined as a ≥50% decrease in Hamilton Rating Scale for Depression (HAM-D) score, and remission was defined according to the criteria of each study (i.e., final HAM-D scores of ≤7–10).

Results: The analysis included 9 open-label studies and a single randomized trial. The open-label studies treated a total of 162 patients, and the randomized trial included 181 patients. The studies all had similar stimulation parameters using the H-coil to induce stimulation over the left dorsolateral prefrontal cortex, usually in 20 sessions. Most of the patients in the open-label studies were treatment-resistant and receiving concurrent antidepressant medication. Two of the studies included patients with bipolar depression.

In the open-label studies, HAM-D scores were significantly reduced after treatment, with an effect size of 2.04. In subgroup analyses, DTMS had larger effects in patients receiving antidepressants than in unmedicated patients. Effects were similar in unipolar and bipolar depression and in patients grouped according to the number of stimuli per session. A total

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of 94 of 150 evaluable patients (60%) in the open-label studies met response criteria, and 35 of 124 (29%) achieved remission. There was no evidence of publication bias in the efficacy results. Of the 162 open-label patients, 27 (17%) dropped out before completing treatment, suggesting a high level of acceptability.

In the randomized trial, DTMS was compared with sham treatment in patients with unipolar depression who were not receiving medication. The treatment effect was smaller (effect size, 0.76) than the open studies combined, but similar to the results in the uncontrolled studies of DTMS monotherapy.

Discussion: The positive effects of DTMS likely resulted from the large volume of cortical stimulation and deeper penetration. However, the large effect size in this analysis may be an overestimate of efficacy based on the open-label nature of the studies. Additional studies with stronger designs are needed.

Kedzior K, Gellersen H, Brachetti A, Berlim M: Deep transcranial magnetic stimulation (DTMS) in the treatment of major depression: an exploratory systematic review and meta-analysis. *Journal of Affective Disorders* 2015;187 (November): 73–83. From the University of Bremen, Germany; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

ECT for Resistant Bipolar Mixed States

In a large prospective study of severe, refractory bipolar mixed states, treatment with ECT produced response or remission in two-thirds of patients.

Methods: Records were reviewed for 197 consecutive patients who received ECT for a current mixed episode during a 5.5-year period at a tertiary-care psychiatric hospital in Italy. Patients who received ≥3 ECT treatments were included in the analysis. All patients had symptoms that were drug resistant, defined as non-responsive to a trial of ≥16 weeks with ≥2 mood stabilizers, antipsychotics, and/or antidepressants. Patients received bilateral ECT twice a week until the treating clinician determined there was a therapeutic response or no further likelihood of improvement. Concomitant medications, other than anticonvulsants, were permitted. All patients were evaluated prior to ECT and 1 week after the final treatment using the 17-item Hamilton Rating Scale for Depression (HAM-D), the Young Mania Rating Scale (YMRS), and the Clinical Global Impression–Severity (CGI-S) and Improvement (CGI-I) scales. Response was defined as a CGI-I rating of much improved or better. Remission was defined as a CGI-I rating of very much improved, a HAM-D score of ≤10, and a YMRS total score of ≤12.

Results: Patients received an average of 7–8 ECT treatments. After treatment, 82 patients (42%) met response criteria, and 60 patients (31%) achieved remission. The mean duration of the current episode was significantly greater for nonresponders than for responders and remitters (13 months vs. 9 and 6 months, respectively; p=0.001). Remission was significantly less likely in patients with comorbid OCD compared with those without (p=0.008). Likelihood of response did not differ according to demographic factors, other comorbid mental illnesses, psychotic symptoms, or the number of previous illness episodes, hospitalizations, or suicide attempts. The number and dosage of ECT treatments also did not differ among the 3 groups. A multivariate analysis showed that, in addition to episode duration and OCD, higher baseline YMRS scores were associated with nonresponse to ECT.

Discussion: Most current guidelines for treating mixed states do not mention ECT, and it is generally viewed as a last resort. Instead, many patients receive treatment for long periods of time with complex, ineffective drug combinations. The present observations suggest that, as

with depression, a long duration of the illness episode may contribute to resistance to ECT and other treatments. The higher baseline YMRS scores in nonresponders confirm previous observations that ECT has a predominantly antidepressant effect in patients with mixed states.

Medda P, Toni C, Mariani M, De Simone L, et al: Electroconvulsive therapy in 197 patients with a severe, drug-resistant bipolar mixed state: treatment outcome and predictors of response. *Journal of Clinical Psychiatry* 2015;76 (September): 1168–1173. From the University of Pisa, Italy; and other institutions. **Source of funding not stated. The authors declared no potential conflicts of interest.**

ECT Efficacy in the Elderly

According to results of a naturalistic study, elderly patients have lower rates of psychiatric rehospitalization than younger patients after ECT for depression, suggesting that the therapy may be a more effective acute treatment strategy in older patients.

Background: Literature on the efficacy of ECT in older patients is sparse and conflicting. While ECT is commonly perceived as particularly beneficial in geriatric depression, it is unclear whether the positive effects endure over time.

Methods: Electronic medical records were reviewed for all patients with a primary diagnosis of major depressive disorder who received an acute course of ECT at a single institution between 2007 and 2011. The primary endpoint was psychiatric rehospitalization, an indicator of relapse or recurrence of severe depressive symptoms. Depression rating scale scores were not available for this study population.

Results: A total of 482 patients received ECT for depression during the study period, 210 of whom were aged ≥65 years. Over the 5-year period, 73 patients were rehospitalized. Overall, rates of rehospitalization were 6% in patients aged ≥65 years and 22% in younger patients (adjusted hazard ratio,* 0.29; $p<0.0001$). About 60% of the rehospitalized patients were readmitted during the first 6 months after ECT, and 77% within 1 year. Differences between older and younger patients in rehospitalization rates were statistically significant as early as 6 months. Among patients who were rehospitalized, older persons had a shorter median interval before relapse: 57 versus 120 days. Rehospitalization did not differ according to gender or the number of ECT treatments received.

Discussion: ECT may be more effective in older patients because biological factors are more prominent in late-life depression, while psychosocial factors play a larger role in younger patients. ECT is also more likely to be used as a first- or second-line treatment in older patients; thus younger patients may have had more severe or refractory depression. A notable finding of this study is the low rate of relapse overall, which cannot be explained entirely by underestimation due to loss to follow-up or the use of rehospitalization as a proxy measure for relapse.

Rosen B, Kung S, Lapid M: Effect of age on psychiatric rehospitalization rates after electroconvulsive therapy for patients with depression. *Journal of ECT* 2015; doi 10.1097/YCT.0000000000000271. From the University of California San Francisco; and the Mayo Clinic, Rochester, MN. **Source of funding not stated. The authors declared no competing interests.**

***See Reference Guide.**

Multimodal Treatment of Adult ADHD

In a randomized trial, combining psychological treatments with methylphenidate produced long-term benefits in adults with ADHD.

Methods: Adults with a confirmed diagnosis of ADHD (n=419; mean age, 35 years) were randomly assigned to 1 of 2 psychological therapies plus either concomitant methylphenidate (*Ritalin*) or placebo. A highly-structured cognitive-behavioral group psychotherapy (GPT) was delivered according to a manualized protocol in groups of 6–9 patients. The control

psychological therapy comprised 15–20 minutes of nonspecific individual counseling. Both treatments were provided in 12 weekly sessions followed by 10 monthly sessions, over a total of 52 weeks. Methylphenidate was started at 10 mg/day and titrated to ≤60 mg/day. The primary aim of the study was to evaluate the effect of combined GPT and methylphenidate on change from baseline to week 12 (following intensive treatment) in the blinded observer-rated Conners Adult ADHD Rating Scale (CAARS). One-year outcomes were also assessed.

Results: Overall, outcomes did not differ significantly among the group that received GPT plus methylphenidate and the other 3 groups. Therefore, separate 2-way comparisons of the 2 psychological treatments and of methylphenidate versus placebo were conducted. The efficacy of GPT did not differ from individual counseling. Symptoms decreased significantly more in the patients who received methylphenidate than in those who received placebo (p=0.003). The advantage of methylphenidate over placebo persisted over the year of treatment. Methylphenidate was superior to placebo in both the GPT and the individual counseling subgroups. Treatment response, defined as a ≥30% decrease in CAARS ADHD Index score, was evident in 24–47% of patients at week 12. (See table.) At 12-month follow-up, rates were no longer significantly different among groups.

Treatment Response by Group Assignment

	Week 12 (n=352)	Week 24 (n=304)	Week 52 (n=243)
GPT + Methylphenidate	30%	46%	51%
GPT + Placebo	24%	33%	44%
CM + Methylphenidate	47%	59%	53%
CM + Placebo	33%	34%	47%

GPT vs. CM at 12 weeks; p=0.009
Methylphenidate vs. placebo at 12 weeks; p=0.05
Methylphenidate vs. placebo at 24 weeks; p=0.001

Discussion: In this study, the control psychological intervention was as effective as the more intensive intervention. Apparently a highly structured group approach is not necessary to produce optimal outcomes. The study supports the long-term benefit of methylphenidate, particularly when used in combination with a psychological approach.

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

Philipsen A, Jans T, Graf E, Matthies S, et al: Effects of group psychotherapy, individual counseling, methylphenidate, and placebo in the treatment of adult attention-deficit/hyperactivity disorder: a randomized clinical trial. *JAMA Psychiatry* 2015; doi 10.1001/jamapsychiatry.2015.2146. From the University of Oldenburg, Germany; and other institutions. **Funded by the German Federal Ministry of Education and Research. Twelve of the 27 study authors disclosed financial relationships with commercial sources.**

***See Reference Guide.**

Bipolar Disorder Guideline

The Florida Best Practice Psychotherapeutic Medication Guidelines for Adults offer simple, evidence-based approaches for front-line clinicians treating patients with bipolar disorder, schizophrenia, and treatment-resistant depression in the community. The bipolar disorder section of the guideline, updated in 2014, was constructed at a consensus meeting of stakeholders, including experts in bipolar disorder, schizophrenia, and major depression; Medicaid drug management leaders; physicians in community mental health centers and private practice; pharmacists; academics; and representatives of managed care. Guideline development was led by Florida Medicaid, a major payer, but cost considerations do not figure in the recommendations.

The 2014 revision includes updated evidence on treatments and also reflects changes in DSM-5. The bipolar disorder guideline is structured to encourage evidence-based safe prescribing first. It differs from other guidelines in giving major consideration to the harms as well as the benefits of medications. The guideline also recommends careful assessment, treatment of comorbidities, and use of symptom measurement scales, and it includes a list of recommended scales and urges their integration into routine clinical practice. The full bipolar disorder guideline can be viewed at http://medicaidmentalhealth.org/ViewGuideline.cfm?GuidelineID=76.

Ostacher M, Tandon R, Suppes T: Florida best practice psychotherapeutic medication guidelines for adults with bipolar disorder: a novel, practical, patient-centered guide for clinicians. *Journal of Clinical Psychiatry* 2015; doi 10.4088/JCP.15cs09841. From the VA Palo Alto Health Care System, CA; and other institutions. **Funded by the Florida Medicaid Drug Therapy Management Program for Behavioral Health; and other sources. One study author disclosed financial relationships with commercial sources; the remaining 2 authors declared no conflicts of interest.**

Measurement-Based Treatment for Depression

In a randomized trial in patients with depression, measurement-based care in which treatment decisions were made using guidelines and rating scales led to significantly more frequent and more rapid response and remission than standard care.[1]

Background: Measurement-based care was first described more than a decade ago by the Texas Medication Algorithm Project and the German Algorithm Project. The algorithms require clinicians to regularly assess illness symptoms and adverse drug effects and recommend adjustment of medications using specific algorithms. The approach has not become mainstream, in part because of a paucity of evidence. This study appears to be the first controlled trial to assess the effect of measurement-based care in patients with major depression.

Methods: Study participants were adults, aged 18–65 years, seeking psychiatric treatment for nonpsychotic major depression at an urban teaching hospital. Subjects were required to have a baseline 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥17 and to undergo a 1-week washout of previous antidepressants. All study patients received open-label treatment with either paroxetine or mirtazapine based on their clinician's choice. Randomly assigned measurement-based care or treatment as usual were delivered by separate treatment teams. Patients who received measurement-based care were seen in the clinic every 2 weeks, where they completed the Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR). Based on whether their scores indicated remission, partial response, nonresponse, or intolerable side effects, they could be continued on their medication, have a dosage change, or be switched to the alternate medication. Primary outcome measures were response (≥50% decrease in HAM-D score) and remission (HAM-D of ≤7). The measurement-based treatment schedule covered 12 weeks, and final outcomes were assessed at 24 weeks by raters unaware of patients' treatment assignment.

Results: A total of 120 patients received randomized treatment. Rates of discontinuation did not differ statistically between the 2 groups: 28% with measurement-based care and 37% with standard treatment. Medication adherence was virtually 100% in both groups. There were twice as many medication changes with measurement-based care (40 dosage adjustments and 4 medication switches) as with treatment as usual (22 dosage changes and 1 switch). Antidepressant dosages were significantly higher in the measurement-based treatment group, beginning at week 2 ($p \leq 0.02$).

Measurement-based care had superior efficacy (see table, next page), and nearly all patients assigned to measurement-based care who experienced response also experienced remission. The number needed to treat* was 5 for response and 3 for remission. The proportion and type of adverse events did not differ between the 2 treatment approaches.

Efficacy Outcomes at 24 Weeks in Patients with Major Depression			
	Measurement-Based Care	**Standard Treatment**	**Significance**
Response	87%	63%	p=0.002
Remission	74%	29%	p<0.001
Mean Time to Response	5.6 weeks	11.6 weeks	p<0.001
Mean Time to Remission	10.2 weeks	19.2 weeks	p<0.001

Editorial.[2] The present study was able to isolate the effect of management-based care by using the same starting medications and the same dosage ranges in both groups. The benefits of measurement-based care are largely attributable to more aggressive, but still patient-tailored, dosing. It appears that patient-reported standardized measures perform as well as clinician ratings and can be implemented efficiently in the clinic, making measurement-based care an approach that improves outcomes without using more resources.

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

[1]Guo T, Xiang Y-J, Xiao L, Hu C-Q, et al: Measurement-based care versus standard care for major depression: a randomized controlled trial with blind raters. *American Journal of Psychiatry* 2015;172 (October):1004–1013. From Capital Medical University, Beijing, China; and other institutions. **Funded by the National Science and Technology Major Projects for Major New Drugs Innovation and Development; and other sources. One study author disclosed financial relationships with commercial sources; the remaining 11 authors declared no competing interests.**

[2]Rush A: Isn't it about time to employ measurement-based care in practice? [editorial] *American Journal of Psychiatry* 2015;172 (October): 934–936. From the Duke–National University of Singapore Graduate Medical School, Singapore. **The author declared financial relationships with commercial sources.**

Common Drug Trade Names*: mirtazapine—*Remeron*; paroxetine—*Paxil

***See Reference Guide.**

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

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

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

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

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Behavioral Therapy for Tic Disorders

Historically, tic disorders have been managed with psychotropic drugs such as antipsychotics and alpha-2 agonists. These treatments have small-to-moderate effects, leaving patients with residual troublesome tics; and they have side effects that may limit long-term use. A review of studies evaluating persistent motor/vocal tics or Tourette's disorder provides evidence-based support for behavioral therapies and outlines some of the challenges to implementing these treatments.

Several types of behavioral intervention (e.g., habit reversal training [HRT], mass negative practice, awareness training, exposure and response prevention) have been investigated for the treatment of tics. Of these, only HRT and its successor, the Comprehensive Behavioral Intervention for Tics (CBIT), have consistently demonstrated efficacy in both adults and children in randomized clinical trials and meta-analyses. The therapies vary in content, but the core components are awareness training, competing response training, and social support. CBIT adds relaxation training, behavioral rewards, and interventions to mitigate daily life factors that can exacerbate symptoms. CBIT produced a positive response in >50% of patients in large-scale controlled trials. A meta-analysis of randomized trials of behavior therapy showed it to be associated with moderate-to-large effect sizes* of 0.67–0.94, with a number needed to treat* of 3 to produce a treatment response, and an odds ratio* for response of 5.8 relative to comparison conditions.

Although behavioral therapies are established, evidence-based interventions for persistent tic disorders, several challenges prevent widespread use. Many clinicians have concerns that the treatments may have unintended negative consequences, such as a rebound effect or symptom substitution. These concerns are not supported by evidence. Access is limited by the shortage of clinicians trained in evidence-based behavioral practice. To improve access, additional clinician training opportunities are being developed by the Tourette Association of America and the CDC. In addition, novel delivery methods, such as intensive treatment

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protocols and telemedicine, are also in development. Professionals from non-mental health disciplines, such as physical therapists, are exploring the possibility of conducting behavioral therapy for persistent tic disorders.

Even when available, behavioral therapies often do not result in complete remission of tics. Adjunctive therapies are being explored to increase the therapeutic response, including acceptance and commitment therapy, methylphenidate in patients with co-occurring ADHD, and cognitive enhancers such as cycloserine. In order for patients to achieve their best outcome, the focus of treatment should be expanded from simply reducing tic severity to improving coping skills, reducing impairment, and improving quality of life.

McGuire J, Ricketts E, Piacentini J, Murphy T, et al: Behavior therapy for tic disorders: an evidence-based review and new directions for treatment research. *Current Developmental Disorders Reports* 2105;2 (December):309–317. From the University of California Los Angeles; and other institutions. **Funded by the NIMH; and other sources. Four study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

Common Drug Trade Names: **cycloserine—***Seromycin***; methylphenidate—***Ritalin*

***See Reference Guide.**

Biomarkers for Bipolar Disorder

Results of a 3-stage discovery, validation, and application study provide preliminary evidence supporting a diagnostic panel of blood biomarkers for bipolar disorder. This finding has the potential to lead to a low-cost blood test that could be routinely used to diagnose bipolar disorder before manic or hypomanic symptoms develop.

Methods: The initial, discovery stage of the research was a meta-analysis of 8 case-control studies. The analysis combined data on serum samples obtained from 183 patients with bipolar I or bipolar II disorder, regardless of present mood state, and 149 age- and gender-matched controls. Samples were assayed for analytes (i.e., peptides and small molecules) that could be combined into a panel that would discriminate patients from controls with high sensitivity and specificity. The resulting panel of markers was then validated in a European case-control study in a similar group of participants, 66 with bipolar disorder and 44 controls. In the application stage, the biomarker panel was tested using data from 3 nested case-control studies: an ongoing Dutch cohort study and 2 U.S. military cohort studies. The number of analytes investigated in the different study samples ranged from 147 to 257, of which 87, plus the 2 covariates (age and gender), were common to all studies. Statistical modeling was used to select a panel of markers that would identify bipolar disorder with high sensitivity and specificity.

Results: The discovery stage identified a panel of 20 analytes with excellent predictive performance. Eleven of the analytes were found to play a role in the inflammatory cascade, including 7 pro-inflammatory and 4 anti-inflammatory markers. Seven analytes were lipid transport-related proteins or proteins with metalloendopeptidase activity. A panel of the 16 available analytes performed well in the validation study. (See table.)

The application stage tested the performance of the panel earlier in the disease course, before patients received a psychiatric diagnosis. The Dutch study included

Analytes Included in the Diagnostic Biomarker Panel

Angiotensin-Converting Enzyme (ACE)	Lipoprotein (a)
Apolipoprotein A1	Macrophage Inflammatory Protein-1 beta
Apolipoprotein A2	Matrix Metalloproteinase-3
CD40 Ligand	Matrix Metalloproteinase-7
CD5	Matrix Metalloproteinase-9, total
Cystatin C	Receptor for advanced glycosylation end products
EN-RAGE	Serum Amyloid P-Component
Hepatocyte Growth Factor	Tumor Necrosis Factor Receptor-Like 2

102 patients with first-episode major depression, of whom 12 received a diagnosis of bipolar disorder within 2 years of sample collection. Performance of the biomarker panel was "good", increasing to "excellent" with the addition to the model of scores on the Inventory of Depressive Symptoms. By itself, this symptom inventory showed only fair performance.

The U.S. military sample included 110 patients with pre-diagnostic bipolar disorder, 75 with schizophrenia, and 184 controls. Overall, the discriminatory performance of the panel was "fair". However, the panel accurately distinguished patients with bipolar disorder from those who went on to receive a diagnosis of schizophrenia but performed no better than chance in distinguishing pre-diagnosis schizophrenia patients from controls.

Discussion: Bipolar disorder is associated with long diagnostic delays and, often, counter-productive antidepressant treatment. The most appropriate time to test for bipolar biomarkers is when patients present with a first depressive episode. The biomarker panel identified in this study is not practical for routine screening because of the low prevalence of bipolar disorder in first-episode depression. However, the results do provide some insights into the pathophysiology of bipolar disorder that may lead to identification of a definitive, clinically useful biomarker signature for the disorder.

Haenisch F, Cooper J, Reif A, Kittel-Schneider S, et al: Towards a blood-based diagnostic panel for bipolar disorder. *Brain, Behavior, and Immunity* 2015; doi 10.1016/j.bbi.2015.10.001. From the University of Cambridge, U.K.; and other institutions. **Funded by the Stanley Medical Research Institute; and other sources. Four study authors disclosed financial relationships with commercial sources; the remaining 11 authors declared no competing interests.**

Self-Help Interventions for Psychosis

According to a meta-analysis, self-help interventions for psychosis are associated with small-to-moderate positive effects, indicating that they have potential for further development.

Background: Self-help interventions (e.g., psychoeducation, peer support groups, cognitive behavioral therapy [CBT]) are recommended in stepped-care models for treatment of depression and anxiety, but their use in severe mental illnesses such as schizophrenia and bipolar disorder is less common. However, these approaches could help patients address the frequency and control of symptoms; symptom-associated distress or anxiety; self-esteem; low mood; and poor social functioning associated with psychosis. The present analysis was conducted to estimate the effects of self-help interventions on symptoms of psychosis and related phenomena.

Methods: A comprehensive review of the social science literature was conducted to identify studies of self-help interventions (i.e., those designed to be executed predominantly independently of professional contact) conducted in patients experiencing symptoms of psychosis that reported results for a specific symptom domain or for other outcomes associated with psychosis. Three categories of interventions were analyzed as possible mediators of outcome: pure, therapist-guided, and peer-support self-help groups. Interventions were also classified according to theoretical basis: psychoeducational, behavioral, or peer support.

Results: Of 24 studies identified and meeting inclusion criteria, 10 evaluated behavioral interventions, 9 evaluated only psychoeducational interventions, 4 evaluated peer support interventions, and 1 evaluated both psychoeducation and peer-support. Outcome measures (e.g., the Brief Psychiatric Rating Scale; the Positive and Negative Syndrome Scale; and quality of life, depression, and anxiety rating scales) were assessed post-intervention. Follow ups ranged from zero to 52 weeks. Self-help interventions had medium effects on positive symptoms, and small-to-medium effects on both negative and overall symptoms. (See table, next page.) Effects on other outcomes associated with psychosis were modest.

For overall symptoms of psychosis, pure and therapist-guided interventions had similar effects, as did psychoeducational and behavioral interventions. Interventions that incorporated multiple self-help techniques were significantly more effective than those using a single technique (effect sizes, 0.80 vs. 0.16; p<0.001). Interventions delivered face-to-face were not more effective than those delivered remotely.

Effects of self-help interventions on symptoms of psychosis and associated outcomes

Outcome	Number of studies	Pooled sample size	Effect size*
Overall psychosis	19	727	0.33
Positive symptoms	12	395	0.42
Negative symptoms	5	188	0.37
Associated outcomes	18	1327	0.13

Discussion: The development of self-help interventions for psychosis has lagged behind similar efforts for depression and anxiety. Approaches for the different disorders are generally similar, although interventions for psychosis are not as firmly based in CBT, focusing instead on implementing coping strategies such as thought stopping and audio relaxation. The present research indicates that patients with psychosis can influence their symptoms. The authors suggest that self-help interventions be investigated further as part of an early intervention strategy for patients presenting with mild-to-moderate symptoms of psychosis.

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

Scott A, Webb T, Rowse G: Self-help interventions for psychosis: a meta-analysis. *Clinical Psychology Review* 2015;39 (July):96–112. From the University of Sheffield, U.K. **This analysis was conducted without funding. The authors declared no competing interests.**

***See Reference Guide.**

Light Therapy for Nonseasonal Depression

In a randomized controlled trial, bright light therapy, with or without an antidepressant, improved depressive symptoms in a group of patients with nonseasonal major depressive disorder. The combination was more effective than bright light as monotherapy.

Methods: Study participants were adults, aged 19–60 years, with major depressive disorder (DSM-IV-TR) who were medication free for ≥2 weeks prior to randomization. Those with a seasonal pattern of depression were excluded. Patients were randomly assigned to 1 of 4 treatment groups: light therapy plus placebo; 20 mg/day fluoxetine (*Prozac*) plus sham light therapy; both active treatments; or a sham/placebo condition. Light therapy was self-administered at home as 30 minutes of exposure to a fluorescent light box as soon as possible after awakening. The sham treatment was an inactive ion generator, which participants were told was also under investigation. The primary efficacy measure was the Montgomery-Asberg Depression Rating Scale (MADRS), administered after 8 weeks of study treatment. Response was defined as ≥50% reduction in MADRS score, and remission as a MADRS score of ≤10 at study end.

Results: A total of 122 patients received treatment. The study arms that included bright light therapy were superior to the others in terms of MADRS declines and rates of response and remission. (See table, next page.) Effect sizes* for the treatment groups versus placebo were 0.24 for fluoxetine, 0.80 for light treatment, and 1.11 for combination treatment. Bright light and combination therapies diverged statistically from fluoxetine and sham/placebo beginning at 4 weeks. Clinical Global Impression–Improvement scores and scores on the Quick Inventory of Depressive Symptomatology–Self Report showed a similar pattern of effect.

The number needed to treat* to achieve remission was 3.5 for combination therapy relative to sham/placebo. An exploratory analysis found that the season of treatment did not influence the results.

Treatment outcome after 8 weeks of bright light therapy, fluoxetine, combination therapy, or placebo.

Outcome	Placebo	Fluoxetine	Bright Light	Combination	Statistical Comparison
MADRS, Decrease from Baseline	6.5	8.8	13.4	16.9	Light vs. placebo p=0.006 Combination vs. placebo p<0.001 Combination vs. fluoxetine p=0.02
MADRS Response	33%	29%	50%	76%	Combination vs. placebo p=0.005
MADRS Remission	30%	19%	44%	59%	Combination vs. placebo p=0.02

Discussion: Previous studies of light therapy for nonseasonal depression have been brief in duration and/or not well controlled. The present study may provide the first high-quality evidence of its efficacy. The poor showing of fluoxetine may have been due to the sample size, which was smaller than planned because of slow recruitment. The steady pattern of response to light therapy over time was similar to that seen with antidepressants.

Lam R, Levitt A, Levitan R, Michalak E, et al: Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder: a randomized clinical trial. *JAMA Psychiatry* 2015; doi 10.1001/jamapsychiatry.2015.2235. From the University of British Columbia, Vancouver, Canada; and other institutions. **Funded by the Canadian Institutes of Health Research. Four study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

***See Reference Guide.**

Schizophrenia and Dementia Risk

The incidence of dementia was increased 2-fold in adults with schizophrenia in a nationwide population-based study from Denmark.[1] The increased risk could not be attributed to known risk factors for dementia.

Methods: The cohort of this registry-based study consisted of all persons born in Denmark, alive at the start of 1995, and aged ≥50 years at some point between 1995 and 2013. Information about diagnoses of schizophrenia and dementia were obtained from inpatient and outpatient medical records, beginning in 1969. Information on comorbid medical illnesses was also included in the analysis.

Results: Nearly 3-million individuals were observed for up to 18 years. Dementia developed during follow-up in 136,012 people, of whom 944 had schizophrenia. Risk of dementia was elevated in individuals with schizophrenia (relative risk,* 2.13 after adjustment for age and gender). Risk was not altered substantially by adjusting the analysis for comorbid medical illnesses such as diabetes and cardiovascular disease, which are known to be associated with schizophrenia and are risk factors for dementia. The relative risk decreased somewhat but remained significantly elevated after adjustment for substance abuse (relative risk, 1.71). The cumulative incidence of dementia by age 65 years was 1.8% for persons with schizophrenia and 0.6% for those without. By age 80 years, the rates were 7.4% and 5.8%, respectively.

Discussion: One proposed explanation for the association between schizophrenia and dementia is the "accelerated aging" hypothesis: Schizophrenia reduces life expectancy and may advance the onset of age-related disorders. Cognitive impairment is a core feature of schizophrenia, and patients with this diagnosis also have a higher prevalence of dementia risk factors such as substance abuse and certain medical illnesses. Although risk is increased,

dementia does not develop in the majority of patients. The aberrant neurodevelopmental hypothesis of schizophrenia describes the early cognitive deficits in the first 2 decades of life but does not explain why a minority of patients later experience dementia.[2] This group may have an etiologically distinct condition that is both neurodevelopmental and neurodegenerative.

[1]Ribe A, Laursen T, Charles M, Katon W, et al: Long-term risk of dementia in persons with schizophrenia: a Danish population-based cohort study. *JAMA Psychiatry* 2015;72 (November):1095–1101. From Aarhus University, Denmark; and other institutions. **Funded by the Lundbeck Foundation; and other sources. The study authors reported no conflicts of interest.**

[2]Lyketsos C, Peters M: Dementia in patients with schizophrenia: evidence for heterogeneity [editorial]. *JAMA Psychiatry* 2015;72 (November):1075–1076. From Johns Hopkins University, Baltimore, MD. **One author declared financial relationships with commercial sources.**

***See Reference Guide.**

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

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

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

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

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

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