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Integrated Neurocognitive Therapy in Schizophrenia

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

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

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

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

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

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

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

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

***See Reference Guide.**

Predicting Functional Outcomes of High-Risk States

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

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

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

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

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

CBT App for Opioid Use Disorder

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

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

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

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

Behavioral Addictions in Bipolar Disorder

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

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

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

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

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

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

Complementary Therapies in Pregnancy

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

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

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

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

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

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

***See Reference Guide.**

Adult ADHD Diagnosis: European Consensus

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

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

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

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

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

Accuracy of E-Prescribing Warnings

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

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

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

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

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

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

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

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

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

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