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Behavioral Activation for PTSD

In a randomized trial in veterans with PTSD, behavioral activation was modestly superior to the usual treatment provided in Veterans Administration PTSD specialty clinics. Both types of treatment were associated with improvement, but patients generally remained symptomatic.

Methods: Study participants were 80 veterans of the wars in Iraq and Afghanistan with a diagnosis of PTSD related to military trauma who had primarily been referred for the study by primary care providers. Behavioral activation was based on an 8-session protocol designed for treating depression. Additional PTSD elements included psychoeducation on the disorder and a focus on its association with patterns of avoidance, thought to play an important role in PTSD impairments. Standard care, the control condition, consisted of treatment at either of 2 VA specialty PTSD clinics, where therapists were trained in prolonged exposure or cognitive processing therapy. The VA clinics also offered individual and group-based alternative treatments and coping skills training. To match treatment intensity with the experimental group, participants in the control group were offered a minimum of 6 individual psychotherapy appointments. The primary study outcomes were changes in PTSD-related distress, measured with the Posttraumatic Stress Disorder Checklist-Military Version (PCL-M), and the Clinician-Administered PTSD Scale (CAPS). Outcomes were assessed at the end of treatment (12 weeks) and again after 3 months.

Results: Despite equal access to care, patients in the behavioral activation group received significantly more individual treatment on average than controls (6.6 versus 2.6 sessions during the 12 study weeks; $p<0.001$). Few veterans in the control group chose to receive prolonged exposure or cognitive processing therapy. Levels of PTSD symptoms decreased in both groups. Behavioral activation was associated with larger decreases than control treatment in symptoms measured with the PCL-M self-report ($p<0.01$). However, patients who received behavioral activation did not show greater improvement than controls in the clinician-rated CAPS total score ($p=0.07$); decrease in the CAPS avoidance subscale were significantly larger in the behavioral activation group ($p=0.03$). Average CAPS scores in both groups remained within the clinical range for PTSD both post-treatment and at 3 months. Depression scores also decreased significantly with treatment in both groups, more so with

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behavioral activation (p=0.02); but patients in both groups continued to have moderate depression. Surprisingly, levels of behavioral activation increased to the same extent in both groups. Both groups reported high levels of satisfaction with treatment.

Discussion: The study results suggest that behavioral activation may be a viable alternative treatment for patients unwilling or unable to engage in trauma processing therapy. The elements of behavioral activation are easy to implement in a range of health care settings and by providers with varying backgrounds, making it a promising therapy to extend the reach of PTSD treatment.

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

Wagner A, Jakupcak M, Kowalski H, Bittinger J, et al: Behavioral activation as a treatment for posttraumatic stress disorder among returning veterans: a randomized trial. *Psychiatric Services* 2019; doi 10.1176/appi.ps.201800572. From the U.S. Department of Veterans Affairs Portland Health Care System, OR; and other institutions. **Funded by the Veterans Health Administration. Two of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Biomarker for Treatment Resistance in Schizophrenia

White matter regional deficits, which can be calculated from MRI imaging, were associated with treatment resistance in a group of patients with chronic schizophrenia.[1] The deficits were also present in some patients with newly diagnosed, minimally treated schizophrenia, which suggests they are not, or not entirely, a chronic disease effect.

Background: Patients with refractory schizophrenia consistently have an earlier age of onset and more severe cognitive deficits. Therefore it has been suggested that white matter measures, which track with neurodevelopment and cognitive dysfunction, may help identify biomarkers of treatment resistance. The previously conducted ENIGMA study identified a region-specific pattern of white matter deficits.[2] The present study was undertaken to test the hypothesis that this pattern of contrast may represent a mechanism that leads to treatment resistance.

Methods: Study participants were 40 individuals with treatment-responsive schizophrenia, 37 with resistant illness, 45 evaluated within the first 2 weeks of starting treatment, and 78 healthy controls. Resistance was defined according to consensus guidelines and consisted of little response to ≥2 medications (each used ≥12 weeks) with above-threshold Brief Psychiatric Rating Scale and Clinical Global Impression scores. Patients were taking a variety of first- and second-generation medications, including 45 using multiple antipsychotics and 31 taking clozapine (*Clozaril*). The study was conducted in China and limited to ethnic Chinese patients. (Ethnic homogeneity is considered an advantage when investigating possible biomarkers.) Regional white matter fractional anisotropy was generated for 21 major regions of the brain, and a regional vulnerability index (RVI) was calculated based on agreement between an individual's pattern of functional anisotropy in these regions and the expected schizophrenia- related patterns identified in the ENIGMA study.

Results: Patients with schizophrenia had significantly lower whole-brain anisotropy than healthy controls, with significant effects in 4 brain regions. Frontal associative tracts—the anterior corona radiata and the genu of the corpus callosum—showed the largest effects. There were no differences in whole-brain or regional functional anisotropy between patients with treatment responsiveness or resistance or between the treatment-initiation group and healthy controls.

The average RVI was highest in the treatment-resistant-group, followed by the treatment-responsive group, newly treated patients, and healthy controls ($p<0.01$ for all patient groups versus controls). These observations suggest that a higher RVI in chronic illness is associated with treatment resistance and that a higher RVI is not primarily the result of chronic illness

or medication, since it was present in newly treated patients. Higher RVIs in the combined groups of chronic patients versus newly treated patients may indicate additional disease progression or a medication effect.

Discussion: Schizophrenia is associated with a white matter deficit pattern that contributes to core cognitive dysfunctions, especially processing speed deficits. The higher RVI values found in the patient groups may be associated with more severe patterns of neurodevelopmental white matter impairment, which could leave patients more vulnerable to treatment resistance.

[1]Kochunov P, Huang J, Chen S, Yanli L, et al: White matter in schizophrenia treatment resistance. *American Journal of Psychiatry* 2019; doi 10.1176/appi.ajp.2019.18101212. From the University of Maryland School of Medicine, Baltimore; and other institutions. **Funded by the National Key R&D Program of China; and other sources. Four of 23 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Kelly S, et al: Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. *Molecular Psychiatry* 2018; 23:1261–1269.

CBT for Internet Addiction

In a randomized trial, a manualized, CBT-based, short-term treatment for internet and computer addiction (STICA) reduced symptoms of a broad range of internet addictions.

Methods: The study was conducted in men, who represent 90% of people seeking treatment for behavioral addictions. Participants, aged 17–55 years, who met diagnostic criteria for internet addiction according to expert ratings based on the clinician- and self-rated versions of the scale for the Assessment of Internet and Computer Game Addiction (AICA-C and AICA-S) were enrolled from 4 clinics for behavioral addiction in Germany and Austria. STICA is a 15-week treatment consisting of weekly 100-minute group sessions interspersed with 8 hour-long individual sessions to promote motivation. Patients were randomized to receive STICA or to a 15-week waitlist control. The primary study outcome was remission, defined as a score of ≤7 on the AICA-S, a 14-item scale that measures the frequency of 8 different internet activities.

Results: A total of 149 patients (mean age, 26 years) were randomly assigned to STICA or the waiting list. The main types of addictive behavior were online games (57%), generalized internet addiction (21%), pornography (16%), and offline computer games (6%). About half of the men had another mental disorder, typically mild to moderate depression. A total of 100 participants either completed STICA as scheduled (n=47) or completed all assessments as controls (n=53).

Remission was achieved by 50 men who received STICA, compared with 17 waitlisted control patients (69% vs 24%; p≤0.001). After adjustment for age, comorbidity, and other factors, the odds ratio* for remission with STICA was 10.1 (p<0.001). Of 36 patients in the STICA group who were contacted 6 months after the end of treatment, 29 (81%) scored below the cutoff for internet addiction. Differences in secondary endpoints, including clinician-rated symptoms, time spent online, and psychosocial function, also favored the STICA group.

Discussion: Whether internet addiction should be defined broadly or narrowly has been controversial. Results of this study support a broad definition. The authors also note that many of the patients were ambivalent toward engaging in treatment. This resistance is a core characteristic of internet addiction and necessitated the inclusion of motivational therapy sessions in the treatment protocol. Although preliminary, these positive results suggest additional research comparing STICA with active control conditions is warranted, particularly evaluating the long-term efficacy of STICA and addressing specific symptom groups.

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

Wölfling K, Müller K, Dreier M, Ruckes C, et al: Efficacy of short-term treatment of internet and computer game addiction: a randomized clinical trial. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.1676. From the University Medical Center of the Johannes Gutenberg-University Mainz, Germany; and other institutions. **Funded by the German Research Foundation. The authors declared no competing interests.**

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Physician Characteristics and Telemental Health

The practice of telemental health is growing rapidly in the U.S., but little is known about which clinicians make use of the technology. A random sample of Medicare claims coupled with linked clinician and practice data were examined in an effort to clarify the characteristics of telemental health providers.

The 20% random sample of Medicare claims for psychiatric evaluation or care identified nearly 29,000 psychiatrists who provided services in 2014–2016. Data on practice location, size, and composition as well as physician characteristics (e.g., gender, years in practice, medical school type) were extracted from linked databases. Over the 2-year period, nearly 378,000 telemental health visits were recorded by 1544 psychiatrists; 40% of whom provided ≥100 of these visits. Compared with psychiatrists who did not offer telemental health services, those who did were younger, and less likely to have peer-reviewed publications or a solo practice. In addition, they were significantly more likely to practice in rural areas (24% vs 6%; $p<0.001$). States with the highest rates of telemental health availability were North Dakota (24%), Wyoming (20%), and Montana (15%), while the lowest rates were generally found in North Eastern states (e.g., Massachusetts, Connecticut, New Jersey, Vermont, and New York at ≤1.5% each). No consistent associations were found between gender, location of medical school, or size and composition of practice.

Based on this sample, it appears that younger physicians in rural locations are the most likely to offer telemental health services. This may be due in part to the geographical barriers to treatment in these areas, and is consistent with data showing younger physicians are more likely to adopt technological innovations.

Choi S, Wilcock A, Busch A, Huskamp H, et al: Association of characteristics of psychiatrists with use of telemental health visits in the medicare population. *JAMA Psychiatry* 2019; 76 (June):654–657. From Wellesley College, MA; and other institutions. **Funded by the NIMH. The authors declared no financial relationships with commercial sources.**

Cannabis and Psychosis Outcomes

In a 10-year longitudinal study, patients with first-episode psychosis who quit smoking cannabis had similar clinical and functional outcomes to those who were not smoking at baseline. Those who continued using cannabis had poorer outcomes than those who stopped.

Methods: Study participants were enrolled in an ongoing study of first-episode psychosis at a regional hospital in Spain. Patients entered the cohort at ages 15–60 years, had no or minimal prior exposure to antipsychotic drugs, and received a diagnosis of schizophrenia, schizophreniform disorder, brief psychosis, psychosis NOS, or schizoaffective disorder. Symptoms were assessed using standard clinical measures. All patients underwent a baseline neuropsychological evaluation about 10 weeks after study entry, when they were most likely to be stabilized. All patients were invited to return for an evaluation 10 years after study intake. Cannabis use was ascertained at baseline and follow-up by interviewing patients and their families.

Results: Of 307 patients who entered the study, 209 were assessed after 10 years. At baseline, 79 of these patients (38%) were cannabis users, smoking an average of 26 joints per week. Cannabis users were younger than nonusers, more likely to be male, and had a lower mean IQ and level of education. They also had a younger age of psychosis onset, more severe positive symptoms, more severe general psychopathology, and higher consumption of other substances (e.g., alcohol, amphetamines, cocaine, LSD).

By the 10-year follow-up, only 15 individuals were still using cannabis. Except for tobacco, cessation of other substance use was also high. After 10 years, statistically significant differences

were observed between persistent cannabis users and the other 2 groups in psychosis symptoms, indicating poorer outcomes in continuing users. (See table.) There were no differences in psychosis symptoms or function between ex-users and never-users. The 3 groups had similar performance on most of the neurocognitive tests, but ex-users had significantly better performance on the attention domain than never-users.

Significant differences in outcomes after 10 years: cannabis users, former users, and never users

Variable	Cannabis users	Ex-users	Never users	Significance (users vs past and never users)
Brief Psychiatric Rating Scale	43.6	30.87	31.42	p≤0.001
Scale for Assessment of Positive Symptoms	4.6	1.53	1.33	p=0.002
Scale for Assessment of Negative Symptoms Positive Dimension	3.13	0.96	0.82	p=0.001
Scale for Assessment of Negative Symptoms Disorganized Dimension	1.47	0.56	0.51	p=0.046

Discussion: It is unclear whether patients were using cannabis before the onset of psychosis symptoms or if those with more severe initial symptoms were using cannabis to self-medicate at baseline. Regardless, these results suggest that at least some of the harmful effects of cannabis use on mental health can be reversed with cessation of use.

Setién-Suero E, Neergaard K, Ortiz-García de la Foz V, Suarez-Pinilla P, et al: Stopping cannabis use benefits outcome in psychosis: findings from 10-year follow-up study in the PAFIP-cohort. *Acta Psychiatrica Scandinavica* 2019; doi 10.1111/acps.13081. From the Marques de Valdecilla University Hospital, Santander, Spain; and other institutions. **Source of funding not stated. The authors did not include disclosure of potentially relevant financial relationships.**

Altered Gene Expression in Major Psychosis

Dysregulated genes and gene networks were identified in the peripheral blood of patients with bipolar disorder in a meta-analysis of multiple data sets. These genes were involved in mechanisms that may underlie the disorder, including oxidative stress, immune signaling, and apoptosis. A risk scoring method developed for the study was capable of discriminating between bipolar disorder and schizophrenia, despite both disorders having similar gene expression.

Methods: The analysis of bipolar disorder was based on all publicly available transcriptome-wide gene expression data from peripheral blood. Data from 7 studies were available, with 95 patients with bipolar disorder and 111 unaffected comparison subjects. The analysis of schizophrenia was based on 258 patients and 241 unaffected comparison subjects from the authors' previous research. The relationship of each gene to bipolar diagnostic status was modeled, and each overexpressed gene was then included in a meta-analysis. Effects of gene regulatory networks were analyzed in multivariate models comparing bipolar cases with controls, bipolar to schizophrenia cases, and bipolar plus schizophrenia cases (together called major psychosis) to the combined set of controls. The authors also developed an approach analogous to risk scoring, called polytranscript scoring, to act as a predictor of disease.

Results: The meta-analysis identified 19 genes significantly differentially expressed in bipolar patients relative to controls: 6 that were over-regulated and 13 that were under-regulated. Three of the 19 genes were also dysregulated in schizophrenia cases, not more than would be expected by chance. Sixty gene sets were differentially expressed in bipolar disorder: 30 over- and 30 under-expressed. The over-expressed sets included immune and cytokine signaling, cell

adhesion, pro-apoptotic signaling, and regulation of reactive oxygen species. Down-regulated functions included regulation of transcription nuclear export of RNA and splicing, DNA repair, and histone modification. Four gene modules, out of 24 investigated, were significantly differently expressed in bipolar disorder. The most significantly over-represented gene sets were found within a single module and were related to various immune functions.

In major psychosis (the combined group of bipolar and schizophrenia cases) 13 gene modules had significant overexpression relative to unaffected comparison subjects. None of these modules showed a significant difference between bipolar and schizophrenia cases. Genes involved in histone modification, apoptosis, and immunity were similarly dysregulated in the 2 disorders.

A machine learning method based solely on gene expression profiles in peripheral blood was able to distinguish patients with bipolar disorder from controls with an area under the curve* (AUC) of 0.724 and from patients with schizophrenia with an AUC of 0.677. Polytranscript risk scoring, which computes a risk score based on expression across many genes, also performed better than chance, with AUCs of 0.672 for distinguishing patients with bipolar disorder from controls and 0.607 for patients with schizophrenia.

Discussion: Although definitive conclusions cannot be drawn about the effects of antipsychotic medications on gene expression, the abnormal expressions in immune, oxidative stress, and apoptotic genes found in the study do not appear to be consistent with reported medication effects. The study findings do indicate that bipolar disorder and schizophrenia share similar gene expression changes and point toward specific pathways for the development of major psychoses: dysregulation in immune signaling, apoptosis, oxidative stress, and chromatin remodeling. However, the authors caution that the models should be further tested and potentially refined with longitudinal data to ensure that they yield both reliable and clinically useful information.

Hess J, Tylee D, Barve R, de Jong S, et al: Transcriptomic abnormalities in peripheral blood in bipolar disorder, and discrimination of the major psychoses. *Schizophrenia Research* 2019; doi 10.1016/j.schres.2019.07.036. From SUNY Upstate Medical University, Syracuse, N.Y.; and other institutions. **Funded by the National Institute on Aging; and other sources. The authors declared no competing interests.**

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Area Under the Curve (AUC): A statistical measures of discrimination—i.e., the ability to correctly classify those with and without a disease. An AUC value of 1 represents perfect accuracy, while a value of 0.5 has accuracy that is no better than chance.

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 >1 indicates that the event is more likely to occur in that group than in the comparison group.

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