Department of Psychiatry

RESEARCH WATCH

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Journals covered in the issue:
* American Journal of Psychiatry (AJP)
* JAMA Psychiatry (JAMA-P)
* The Journal of Clinical Psychiatry (JCP)
* Lancet Psychiatry (LP)
* Journal of the American Academy of Child & Adolescent Psychiatry (JAACAP)
* Acta Psychiatrica Scandinavica (APS)

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Highlights

- A large prospective cohort study suggests that exercising as little as an hour per week provides protection against future depression but not anxiety. (AJP)

- Data from two waves of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) suggests that cannabis use is associated with increased risk of non-medical opioid use. (AJP)

- Genetic risk score for schizophrenia is inversely associated with lithium treatment response in patients with bipolar disorder; genetic variants related to HLA antigen complex and inflammatory cytokines appear to be involved in this relationship. (JAMA-P)

- Low episodic memory scores in subjects without dementia emerge 10-15 years after the onset of amyloid positivity, and have limited value as a screening tool for early Alzheimer disease process. (JAMA-P)

- Comorbid circadian rhythm sleep-wake disorders could be a significant predictor of relapse in euthymic bipolar disorder patients. (JCP)

- RCT suggests benefits of galantamine and computerized CBT for reducing cocaine use in subjects with cocaine dependence. (JCP)

- AVATAR therapy, in which people with auditory hallucinations have a dialogue with a digital representation of their presumed persecutor, shows efficacy over supportive counseling for the treatment of auditory hallucinations in an RCT. (LP)

- PANSS-8 and PANSS-6, shorter versions of the 30-item Positive and Negative Syndrome Scale (PANSS-30), show high correlation with PANSS-30, and early improvement on all 3 scales predicts subsequent response and remission. (APS)

- Cognitive behavioral therapy for adult ADHD, added to treatment as usual, shows significant improvement in ADHD symptoms in RCT. (APS)

- Cohort study from Taiwan suggests that adolescents and young adults with ADHD are at higher risk of sexually transmitted infections than those without ADHD, and treatment with ADHD medications may lower this risk. (JAACAP)

The American Journal of Psychiatry
Volume 175, Issue 1

Exercise and the Prevention of Depression: Results of the HUNT Cohort Study
Harvey, et al.

This large prospective cohort study investigated the longitudinal protective effects of exercise against new onset depression and anxiety, the amount and intensity of exercise that provides protection, and the underlying mechanisms for this association. A population-based health survey conducted in rural Nord-Trøndelag County of Norway was utilized to follow healthy adults (N=33,908) without symptoms of mental or physical illness at study onset for approximately 11 years from 1984-86 through 1995-97. Participants completed questionnaires on depression and anxiety symptoms, psychological and physical health, and level and intensity of exercise at baseline and follow-up sessions. Results suggested that a relatively low amount and intensity of exercise can provide significant protection against later depression, but not anxiety. After adjusting for confounders, individuals who reported no exercise at baseline had 44% increased odds of developing depression compared to those who reported exercising at least 1-2 hours per week.

Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States
Olfson, et al.

Data collected from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) at wave 1 (2001-2002) and wave 2 (2004-2005) were assessed to determine the relationship between cannabis use and incident nonmedical prescription opioid use, and whether there was a subsequent decrease in nonmedical opioid use in adults using cannabis and nonmedical prescription opioids. NESARC data were gathered through structured interview and included information on opioid and other substance use disorders, mood and anxiety disorders, family substance use, frequency of cannabis use, and pain levels, over the previous year in this nationally representative sample (N=34,653). Logistic regression models indicated that cannabis use at wave 1 was associated with a significant increase in the odds of prevalent nonmedical prescription opioid use (OR= 5.78, 95% CI= 4.23-7.90) and use disorder (OR=7.76, 95% CI= 4.95-12.16) at wave 2, which persisted when adjusting for covariate factors. For those with pain at wave 1, cannabis use was associated with increased incident nonmedical opioid use at wave 2 (adjusted OR= 2.99, 95% CI= 1.63-5.47). In individuals with nonmedical opioid use at wave 1, cannabis use was associated with an increase in nonmedical opioid use at wave 2 (adjusted OR=3.13, 95% CI=1.19-8.23).

Dissociation in Psychiatric Disorders: A Meta-Analysis of Studies Using the Dissociative Experiences Scale
Lyssenko, et al.

This meta-analysis aimed to provide an evidence base for the prevalence and distribution of dissociative experiences in adults with psychiatric disorders. Searching several online databases for primary studies

using the Dissociative Experiences Scale (DES) I or II, or the German version of this scale in individuals with mental disorders initially yielded 1,907 articles. These were further screened systematically and, ultimately, 216 articles evaluating 15,219 total individuals were included. Data (including diagnostic group, mean and SD of the dissociation score, and number of participants) were extracted by independent raters and agreed upon systematically or by discussion in cases of discrepancy. Resulting meta-analytic statistics showed that the highest mean dissociation scores were found for dissociative identity disorders (mean 48.7, 95% CI=46.4, 50.9), PTSD (mean 28.6, 95% CI=25.6, 31.5), borderline personality disorder (mean 27.9, 95% CI= 25.3, 30.6), followed by conversion disorder (mean 25.6). Patients with bipolar disorders had the lowest dissociation scores (mean 14.8).

Increased Risk of Smoking in Female Adolescents Who Had Childhood ADHD
Elkins, et al.

Prospective and twin difference methods were combined to investigate the etiology of adolescent smoking in twins discordant for ADHD. Data sets from three cohorts were combined (N=3762, 52% female) comprising 1,881 same-sex twin pairs (64% monozygotic) in order to allow for adequate statistical power to identify within-pair differences and gender moderation. Data were gathered through parent and child interviews assessing ADHD before age 12, nicotine dependence, lifetime conduct disorder and oppositional defiant disorder, and symptoms were assigned by consensus of individuals with advanced clinical training. Regression models of childhood inattentive and hyperactivity symptoms were used to predict smoking outcomes by age 17. Findings suggested that adolescents with more inattentive or hyperactive-impulsive symptoms were more likely to start smoking and to do so at a younger age without significant gender moderation. Females with ADHD showed faster progression to daily smoking, more cigarettes per day, and more nicotine dependence symptoms as compared to their male counterparts. Monozygotic female twins with more inattention than their co-twins had greater smoking involvement with a possible causal relation, whereas hyperactivity and impulsivity symptoms appeared to be noncausal.

JAMA Psychiatry
Volume 75, Issue 1

Association of Polygenic Score for Schizophrenia and HLA Antigen and Inflammation Genes With Response to Lithium in Bipolar Affective Disorder: A Genome-Wide Association Study International
Consortium on Lithium Genetics (ConLi+Gen)

The efficacy of lithium is highly variable, with a non-response rate of up to 30%. There is a genetic overlap between bipolar affective disorder and schizophrenia, this study tested whether a polygenic score for schizophrenia would be associated with treatment responses to lithium in bipolar affective disorder. Thus, 2,586 patients with bipolar disorder who had been treated with lithium were genotyped and assessed for response to treatment. The polygenic score for schizophrenia was inversely associated with lithium treatment response. Patients with bipolar affective disorder who had a low polygenic load for

schizophrenia responded better to lithium (odds ratio 3.46, comparing first decile of polygenic score to the 10th decile). Furthermore, genome-wide association study revealed involvement of genetic variants related to HLA antigen complex and inflammatory cytokines in this relationship.

Utility of Imaging-Based Biomarkers for Glutamate-Targeted Drug Development in Psychotic Disorders A Randomized Clinical Trial
Javitt, et al.

In this study researchers evaluated the utility of 3 potential biomarkers for detecting ketamine-related alterations in brain glutamate:
1) ketamine-evoked changes in fMRI blood oxygen level–dependent response (pharmacoBOLD)
2) glutamate proton magnetic resonance spectroscopy (1H MRS)
3) task-based fMRI
65 healthy volunteers received sequential ketamine or placebo infusions. In pharmacoBOLD, a highly robust and consistent increase (Cohen d = 5.4; $P < .001$) in fMRI response was observed. A smaller but significant signal was also observed in 1H MRS. By contrast, no significant differences in task-activated fMRI responses were found between groups. Study supports use of pharmacoBOLD as a glutamatergic target engagement biomarker in early-phase clinical studies.

Effectiveness of Online Collaborative Care for Treating Mood and Anxiety Disorders in Primary Care: A Randomized Clinical Trial
Rollman, et al.

Objective of this RCT was to examine the effectiveness of combining an internet support group (ISG) with an online computerized cognitive behavioral therapy (CCBT) provided via a collaborative care program for treating depression and anxiety vs CCBT alone and whether providing CCBT in this manner is more effective than usual care. 704 patients were randomized to CCBT alone, CCBT+ISG, or usual care. Patients receiving CCBT+ISG reported similar 6-month improvements in mental health–related quality of life, mood, and anxiety symptoms compared with patients receiving CCBT alone. However, compared with patients receiving usual care, patients in the CCBT alone cohort reported significant 6-month effect size improvements in mood (effect size, 0.31) and anxiety (effect size, 0.26) persisted 6 months later; completing more CCBT sessions produced greater effect size improvements in mental health–related quality of life and symptoms.

Association of Cerebral Amyloid-β Aggregation With Cognitive Functioning in Persons Without Dementia
Jansen, et al.

This cross-sectional, multicenter study attempted to determine whether cerebral amyloid-β aggregation, a key characteristic of Alzheimer disease, is associated with cognitive functioning in persons without dementia. Among 2908 persons with normal cognition (mean age 67.4) amyloid positivity was associated with low episodic memory performance – assessed by a verbal word learning test – after age 70 years

(mean difference in amyloid positive vs negative, 4% at 72 years and 21% at 90 years) but was not associated with low MMSE scores. In 4133 subjects with mild cognitive impairment, amyloid positivity was associated with both low memory and low MMSE scores. Low memory scores emerged 10 to 15 years after the onset of amyloid positivity, and therefore have limited value as a screening tool for early Alzheimer disease process.

The Journal of Clinical Psychiatry
JCP Weekly - 12/26/17 - 1/2/18

Circadian Rhythm Sleep-Wake Disorders Predict Shorter Time to Relapse of Mood Episodes in Euthymic Patients With Bipolar Disorder: A Prospective 48-Week Study
Takaesu, et al.

The authors of this 48-week prospective study set out to determine if there was a predictive correlation between circadian rhythm dysfunction and relapse in euthymic bipolar disorder patients. A total of 104 patients were enrolled in the study, 34 of which met criteria for a circadian rhythm sleep-wake disorder (CRSWD) based off sleep logs. During the 48-week study, 51 patients experienced a relapse of their bipolar symptoms, measured using Montgomery-Asberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) scores every 4 weeks. Multivariate Cox hazard regression analyses revealed that 2 or more previous mood episodes within the past year and comorbidity of CRSWD were significantly associated with the time to relapse of mood episodes ($P < .001$). Comorbid CRSWD, mainly delayed sleep-wake phase disorder, could be a significant predictor of relapse in BD patients

Galantamine and Computerized Cognitive Behavioral Therapy for Cocaine Dependence: A Randomized Clinical Trial
Carroll, et al.

Galantamine is an acetylcholinesterase inhibitor and agonist at nicotinic acetylcholine receptors. This randomized clinical trial assessed whether galantamine alone or in combination with cognitive behavioral therapy (CBT) could be an effective treatment in individuals with cocaine use disorder. Over the course of 12 weeks, 121 people diagnosed with cocaine use disorder were randomly assigned to one of four groups: (1) galantamine (8 mg/d) plus standard methadone maintenance treatment (treatment as usual [TAU]), (2) placebo plus TAU, (3) galantamine plus computerized CBT plus TAU, or (4) placebo plus computerized CBT plus TAU. The primary cocaine use outcome was change in percent days of abstinence over time. Number of cocaine-negative urine toxicology screens submitted, and cognitive function were secondary outcomes. Random effect regression analysis indicated significant reductions in frequency of cocaine use over time, with significant treatment-by-time effects for both galantamine over placebo (p=0.02) and computerized CBT over standard methadone treatment (p=0.04) but no evidence of significant benefit of the combination over either treatment alone. Galantamine did not improve measures of cognitive function in this sample.

Treatment With a Ghrelin Agonist in Outpatient Women With Anorexia Nervosa: A Randomized Clinical Trial

Fazeli, et al.

This randomized, double-blind, placebo-controlled study examined the effects of relamorelin in individuals with anorexia nervosa. Relamorelin, an agonist of the appetite-stimulating hormone ghrelin, is believed to reduce gastric emptying time and lead to weight gain. A total of 22 outpatient women were enrolled in the study, 10 of which who were randomly assigned to relamorelin 100 μg subcutaneously daily (mean ± SEM age: 28.9 ± 2.4 y), and 12 who were randomly assigned to placebo (28.9 ± 1.9 y). Three subjects randomized to relamorelin stopped use of the study medication due to reported feelings of increased hunger. After 4 weeks, there was a trend toward an increase in weight in participants randomized to relamorelin (mean ± SEM change: 0.86 ± 0.40 kg) compared to placebo (0.04 ± 0.28 kg; P = .07), and gastric emptying time was significantly shorter in patients taking relamorelin (median [interquartile range]: 58.0 [51.0, 78.0] minutes) compared to placebo (85.0 [75.8, 100.5] minutes; P = .03). Further study is necessary to determine the long-term safety and efficacy of a ghrelin agonist in the treatment of anorexia nervosa.

The Lancet Psychiatry
Volume 5, Issue 1

AVATAR therapy for auditory verbal hallucinations in people with psychosis: a single-blind, randomized controlled trial.

Craig, et al.

AVATAR therapy, invented by Julian Left in 2008, is a new approach in which people who hear voices have a dialogue with a digital representation (AVATAR) of their presumed persecutor, voiced by the therapist such that the AVATAR responds by becoming less hostile and concedes power over the course of therapy. This single-blind, randomized controlled trial aimed to investigate the effect of AVATAR therapy on auditory verbal hallucinations compared with a supportive counseling control condition. In this study, 150 people were deemed eligible and were randomly assigned to receive either AVATAR therapy (n=75) or supportive counseling (n=75). 124 (83%) met the primary outcome. The reduction in PSYRATS-AH (Psychotic Symptoms Rating Scales Auditory Hallucinations) total score at 12 weeks was significantly greater for AVATAR therapy than for supportive counseling (mean difference -3.82 p<0.0093). There was no evidence of any adverse events attributable to either therapy.

Side-effects associated with Ketamine use in depression: A systematic review

Short, et al.

This systematic review studied the safety of ketamine in the treatment of depression after single and repeated doses. 60 articles met inclusion criteria. After acute dosing, psychiatric, psychomimetic, cardiovascular, neurological, and other side-effects were more frequently reported after ketamine

treatment than after placebo in patients with depression. Side effects most commonly reported by studies (in descending order) were headache (35% of studies), dizziness, dissociation, increased blood pressure, blurred vision, nausea, sedation, light-headedness, anxiety and elevated heart rate (15% of studies). Reporting of side-effects in randomized controlled trials was similar but also included cognitive side effects, urinary tract side effects and dependency risk. Acute side-effects associated with single-dose use in depression are common, but generally transient and resolve spontaneously. Review findings are suggestive of a selective reporting bias with limited assessment of long-term use and safety.

Journal of the American Academy of Child and Adolescent Psychiatry
Volume 57, Issue 1

Sexually Transmitted Infection Among Adolescents and Young Adults With Attention-Deficit/Hyperactivity Disorder: A Nationwide Longitudinal Study
Chen, et al.

This matched-pair longitudinal cohort study investigated the relationship between development of STI among youth with and without ADHD. Youth with ADHD (n=17,898) and age/sex-matched non-ADHD controls (n=71,592) were identified/enrolled using the Taiwan National Health Insurance Research Database. Youth with ADHD developed any STI at a younger age (20.51 vs. 21.90), at a higher incidence (1.2% vs. 0.4%), and with higher risk of subsequent STI (HR 3.36, 95% CI). ADHD was associated with higher prevalence of substance use disorders in men and women vs. matched controls (2.7% vs 0.9% and 1.5% vs 0.3%, respectively). Short- and long term use of ADHD medications decreased risk of STI in males (HR: 0.68 and 0.53, respectively). After adjustment for demographic data, comorbidities, and ADHD medication, an association between substance use disorders and STIs was observed in women only (HR: 3.87).

Brain Structural Correlates of Subclinical Obsessive-Compulsive Symptoms in Healthy Children
Sunol, et al.

The aim of this study was to identify the brain volumetric features associated with subclinical obsessive-compulsive (OC) symptoms, as well as potential modulatory effects of sex and age in a sample of 255 healthy children without special needs or mental health conditions. The 21-item self-reported Obsessive Compulsive Inventory – Child Version (OCI-CV) was used to assess six OC subscales and scores correlated with structural MRI. Ordering symptoms were negatively related to GM volumes of the ventral caudate nuclei in younger boys. Hoarding symptoms were positively associated with regional gray and white matter (GM and WM) volumes in the left inferior frontal gyrus in older children. Obsessing symptoms correlated negatively with GM and WM volumes in the right temporal pole. Doubt-checking correlated positively with WM volumes in the right inferior fronto-occipital fasciculus and the isthmus of the corpus callosum; alternatively, doubt-check correlated negatively with GM volumes in the left middle frontal gyrus.

From Childhood Conduct Problems to Poor Functioning at Age 18 Years: Examining Explanations in a Longitudinal Cohort Study
Wertz, et al.

This longitudinal prospective cohort study investigated the extent to which childhood conduct problems predicted poor functioning in emerging adulthood. Using the Environmental Risk Longitudinal Twin Study (a birth cohort of 2,232 twins [56% MZ, 44% DZ] in England and Wales), conduct problems were assessed initially at age 5 with follow-up visits conducted at ages 7, 10, 12, and 18 with 93% retention. After accounting for concurrent psychopathology in early adulthood and early familial risk factors (genetic and environmental), severe childhood conduct problems were found to increase risk of poor functioning (cautions and conviction, daily cigarette smoking, heavy drinking, and psychosocial difficulties) at age 18 in all functional outcomes. Incidence-rate ratios ranged from 1.36 (overweight) to 3.62 (cautions/convictions). Additional risk factors for childhood conduct problems included SES disadvantage, exposure to violence, and parental psychopathology. Correlations were greater in MZ than DZ twins.

Acta Psychiatrica Scandinavica
Volume 137, Issue 2

Early improvement in PANSS-30, PANSS-8, and PANSS-6 scores predicts ultimate response and remission during acute treatment of schizophrenia
Lin, et al.

This study examined the relationship between the 30-item Positive and Negative Syndrome Scale (PANSS-30) and the shorter PANSS-8 and PANSS-6, which are both derived from the PANSS-30, to determine their relative reliability, validity, and sensitivity in predicting response/remission. Using data from three trials of 270 schizophrenia inpatients receiving antipsychotics indicated internal consistency, validity, sensitivity to change, and scalability between all three instruments. The PANSS-8 and PANSS-6 were both scalable at each assessment, except for baseline assessments using the PANSS-6, indicating that both instruments are clinically useful. Early improvement using PANSS-8 or PANSS-6 had comparable predictive values with that of PANSS-30 for response/remission.

Cognitive–behavioural therapy for adult attention-deficit hyperactivity disorder: a proof of concept randomised controlled trial
Dittner, et al.

Sixty adults diagnosed with ADHD were randomly assigned to treatment as usual (TAU) or to TAU plus sixteen sessions of individual cognitive-behavioral therapy (CBT) for ADHD. Using Barkley Current Symptoms Scale and score on the Work and Social Adjustment Scale, results indicated that adding formulation-based CBT for ADHD to TAU significantly improved ADHD symptoms, as compared to TAU alone. Adjusted effect sizes (ES) were 1.31 and 0.82 respectively. This is the first randomized controlled

trial to provide preliminary evidence of efficacy and acceptability of individual formulation-based CBT for ADHD when added to TAU over TAU alone.