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Research Watch is an initiative by the residents of University Hospitals Cleveland Medical Center/ Case Western Reserve University; it aims to inform psychiatry residents and faculty of notable articles published in prominent research journals.

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)

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Highlights

- RCT shows efficacy of real-time fMRI amygdala neurofeedback in the treatment of major depression. (AJP)
- Fluoxetine (but not CBT) found more effective compared to placebo in RCT for reducing self-report symptoms of hypochondriasis. (AJP)
- Swedish registry study shows 14% reduction in incidence of suicide related events during lithium treatment but not during valproate treatment in bipolar disorder (AJP)
- ECT treatment lowers 30-day psychiatric readmission rate by almost half in US hospitals. (JAMA-P)
- Investigators develop a risk calculator with good discrimination for the prediction of bipolar spectrum disorders for offspring of parents with bipolar disorder. (JAMA-P)
- PET study demonstrates presence of increased neuroinflammation in the cortico-striato-thalamo-cortical circuit in subjects with OCD. (JAMA-P)
- CSF levels of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) appear to be state-dependent markers in MDD. (JCP)
- RCT suggests efficacy of suvorexant, a potent selective orexin receptor antagonist, in preventing delirium in the medically ill. (JCP)
- On comparison of neuropsychological profiles, cognitive deficits in behavioral variant frontotemporal dementia appear to be less severe than cognitive deficits seen in primary psychiatric disorders with active symptoms. (JCP)
- Phase 3 RCT shows deutetrabenazine to be a safe and effective treatment for subjects with tardive dyskinesia. (LP)
- Prospective analysis shows that relapse of psychosis associated with continued cannabis use in first episode psychosis is partly mediated through non-adherence to prescribed antipsychotic medication. (LP)
- RCT comparison of aripiprazole and quetiapine in child and adolescent first episode psychosis shows equal but modest efficacy in reducing positive symptoms, with distinct adverse effects profiles. (LP)
- A retrospective cohort study shows that concomitant SSRI/SNRI use with atypical antipsychotics in youth is associated with heightened risk of type 2 diabetes mellitus. (JAACAP)

The American Journal of Psychiatry

Volume 174, Issue 8

Randomized Clinical Trial of Real-Time fMRI Amygdala Neurofeedback for Major Depressive Disorder: Effects on Symptoms and Autobiographical Memory Recall

Young, et al.

This RCT examined the therapeutic potential of a novel approach known as real time functional MRI neurofeedback (rtfMRI-nf) to enhance the amygdala hemodynamic response to positive memories in depressed individuals. Non-medicated depressed participants were randomly assigned to receive two sessions of rtfMRI-nf from the amygdala (N=19) or from a control region (N=17) in the parietal lobe not involved in emotional processing. The primary outcome measure was change in Montgomery-Asberg Depression Rating Scale (MADRS) score. 12 of the participants in the experimental group demonstrated > 50% decrease in MADRS scores after neurofeedback versus 2 in the control group. At study end, 6 participants in the experimental group met criteria for remission (MADRS < 10) as compared to 1 in the control group, resulting in a number needed to treat of 4.

Randomized Control Trial of Medication and Cognitive-Behavioral Therapy for Hypochondriasis

Fallon, et al.

This RCT (N= 195) compared the effect of placebo, CBT, fluoxetine alone, and joint treatment with fluoxetine and CBT for hypochondriasis over a 24-week period. Responders were defined as having a 25% or greater improvement in both self-report (measured by the Whiteley Index) and objective (H-YBOCS scores) hypochondriacal symptoms from baseline. The Cochran-Armitage trend test assessed the hypothesized pattern of response: joint treatment > CBT or fluoxetine treatment > placebo treatment. The hypothesized pattern of response was found to be statistically significant on analysis: placebo with 29.55%, individual active treatment groups with 41.84%, and joint treatment group with 47.17% response rates. However, while the pattern was significant, responder rates for each individual active treatment were not statistically different from placebo. Analysis of just the self-report measure Whiteley Index demonstrated that fluoxetine (but not CBT) was significantly more effective at reducing hypochondriasis at week 24 compared to placebo.

Suicidal Behavior During Lithium and Valproate Treatment: A Within-Individual 8-Year Prospective Study of 50,000 Patients with Bipolar Disorder

Song, et al.

This longitudinal cohort study used population-based registers in Sweden to allow for within-individual comparisons of 51,535 individuals with bipolar disorder over an 8-year period (2005-2013). The aim was to compare associations of lithium and valproate treatment with suicidal behavior within these individuals during this period. The main outcome was suicide-related events, of which 10,648 occurred during the study timeframe in 4405 individuals eligible for within-individual analysis. There was a 14%

reduction in incidence of suicide related events during lithium treatment but not during valproate treatment, with statistically significant differences in hazard ratios. The population attributable fraction was estimated (based on exposure rate and hazard ratios) to be 12%, suggesting 12% of suicide related events could have been avoided if patients were treated with lithium during the entire follow-up period.

JAMA Psychiatry

Volume 74, Issue 8

Efficacy of a Maternal Depression Prevention Strategy in Head Start: A Randomized Clinical Trial

Silverstein, et al.

Head Start is a federal program which provides comprehensive early childhood education, health, nutrition, and parent involvement services to low-income children and their families. This randomized clinical trial, followed 230 mothers with 6 Head Start agencies, who had depressed mood, anhedonia, or history of depression, randomized to a problem-solving education (PSE) intervention or usual services over a 12-month period. Mothers in a current major depressive episode were excluded. Those receiving problem-solving education experienced fewer number of episodes with depressive symptom elevations (incident rate ratio: 0.60). In analyses stratified according to baseline depressive symptoms, this preventive effect was only significant in those with lower-level baseline symptoms (QIDS score < 11).

Association of Electroconvulsive Therapy with Psychiatric Readmissions in US Hospitals

Slade, et al.

Using data from 162,691 psychiatric inpatients with primary diagnoses of major depressive disorder, bipolar disorder, or schizoaffective disorder from hospitals in 9 states, this study examined the correlation of ECT with 30-day hospital readmissions. The ECT population had a 6.6% readmission rate, as compared with the non-ECT population readmission rate of 12.3% (risk ratio 0.54). The impact on ECT in lowering readmission rates was even greater in individuals with male gender, and in those with diagnoses of bipolar disorder or schizoaffective disorder. This study indicates that ECT may be associated with reduced short-term psychiatric readmissions.

Predict New-Onset Bipolar Spectrum Disorder in Youth at Familial Risk

Hafeman, et al.

The Pittsburgh Bipolar Offspring Study is a longitudinal cohort investigation of offspring of parents with bipolar I or bipolar II disorder, with a mean follow-up period of 9 years. The offspring in this analysis were aged 6-17 years and had not yet developed a bipolar spectrum disorder. Using a risk calculator, which included measures of mood and anxiety, general psychosocial functioning, age at mood disorder onset in the bipolar parent, and age at each visit, the study was able to predict 5-year risk of new-onset bipolar spectrum disorder with good discrimination (time-dependent area under the curve 0.76). In the future, such a calculator may inform clinicians' frequency of monitoring and treatment options.

Inflammation in the Neurocircuitry of Obsessive-Compulsive Disorder

Attwells, et al.

This small case control study attempted to determine whether microglial activation, an important component of neuroinflammation, is increased in the cortico-striato-thalamo-cortical (CSTC) circuit of subjects with OCD. Translocator protein density increases with microglia activation and the translocator protein distribution volume, measured using PET radioligands, is an index of the translocator protein density; the distribution volume was used as a measure of neuroinflammation in this study. Investigators found using PET scan that translocator protein distribution volume was significantly elevated in the CSTC of participants with OCD (N=20) compared with healthy controls (N=20), with a mean difference of 32% in values. The Yale-Brown Obsessive Compulsive Scale measure of distress associated with preventing compulsive behaviors was positively correlated with translocator protein distribution volume in the orbitofrontal cortex ($r=0.62$; $p=0.005$). This is the first study demonstrating increased presence of inflammation within the neurocircuitry of OCD.

Association Between Medication Use and Performance on Higher Education Entrance Tests in Individuals With Attention-Deficit/Hyperactivity Disorder

Lu, et al.

In this Swedish cohort study, registry data was studied to explore the association between use of ADHD medications and academic test performance in young adults. 930 individuals with ADHD (mean age 22 years) were identified who had taken the Swedish standardized test for entry into higher education multiple times during periods with and without ADHD medications. In Sweden there is no restriction on the number of times that one may take the higher education entrance test; universities automatically consider an applicant's best test score. The analysis was made by comparing the test scores within the same individual during their own medicated vs non-medicated periods. Use of ADHD medications was associated with a statistically significant increase of 13.13 points (on a scale of 0-200) in the test scores. The effect was reduced to a 4.80-point increase after adjusting for age and the effect of taking the test multiple times.

The Journal of Clinical Psychiatry

JCP Weekly 7/11/17 - 8/1/17

Preventive Effects of Suvorexant on Delirium: A Randomized Placebo-Controlled Trial

Hatta, et al.

This randomized, placebo-controlled trial examined suvorexant, a potent selective orexin receptor antagonist, as a potential medication for the prevention of delirium. Seventy-two patients between the ages of 65 and 89 admitted to ICU or regular acute wards were randomly assigned to 15 mg/day of

suvorexant (36 patients) or placebo (36 patients) every night for 3 days. Of those who received suvorexant, 0/36 developed delirium vs 6/36 (17%) in the placebo group ($P=0.025$). Larger studies are needed to show the potential of suvorexant to improve the circadian core domain of delirium.

Cognitive Deficits in Patients With Neuropsychiatric Symptoms: A Comparative Study Between Behavioral Variant Frontotemporal Dementia and Primary Psychiatric Disorders

Vijverberg, et al.

This study compared neuropsychological profiles in behavioral variant frontotemporal dementia (bvFTD) with its most common primary psychiatric differential diagnoses, major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia, in older patients with active symptoms. Compared to healthy controls, both the bvFTD and primary psychiatric disorder groups showed significant impairment on all cognitive domains. Executive function was more disturbed in all primary psychiatric disorders compared to bvFTD ($P < .001$). Attention and working memory were significantly better in the bvFTD and schizophrenia groups compared to the MDD and BD groups ($P < .001$). For verbal memory, the bvFTD group scored significantly higher compared to patients with schizophrenia, BD, or MDD ($P < .001$). Overall, cognitive deficits in bvFTD were less severe than cognitive deficits seen in primary psychiatric disorders with active symptoms. This suggests that in the differential diagnosis of bvFTD, presence of cognitive deficits does not rule out primary psychiatric diagnoses.

Relationships of Cerebrospinal Fluid Monoamine Metabolite Levels With Clinical Variables in Major Depressive Disorder

Yoon, et al.

CSF Monoamine metabolite levels were measured to determine if there were correlations with major depressive disorder (MDD) clinical variables, as current clinical significance remains unclear with current research. CSF samples from 75 patients with MDD and 87 healthy controls. Levels of CSF homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) were analyzed by high-performance liquid chromatography and the relationships of the metabolite levels with age, sex, diagnosis, psychotropic medication use, and depression severity assessed. All monoamine metabolites in moderately to severely depressed patients (17-item Hamilton Depression Rating Scale score >12) were significantly lower than those in controls ($P < .0005$ for all 3 metabolites). HVA levels ($\rho = -0.43$, $P < .001$) and 5-HIAA levels ($\rho = -0.23$, $P < .05$), but not MHPG levels ($\rho = -0.18$, $P > .1$), were related to depression severity indicating that CSF 5-HIAA and HVA levels could be state-dependent markers in MDD patients. Since 5-HIAA levels greatly decrease with the use of antidepressants, HVA levels might be more useful in the clinical setting.

Secondary Prevention of Chronic PTSD by Early and Short-Term Administration of Escitalopram: A Prospective Randomized, Placebo-Controlled, Double-Blind Trial

Zohar, et al.

Authors examined whether preventive intervention via early and short-term administration of a

selective serotonin reuptake inhibitor (SSRI), within 1 month of exposure to a traumatic event (before diagnosis of PTSD could be made), may reduce the severity of PTSD at 13 months' follow-up. Among 353 participants, patients were randomly assigned to escitalopram (n=176) or placebo (n=177). Early and short-term administration of escitalopram was not shown to prevent PTSD, although it did improve sleep quality. In a subgroup of participants who experienced intentional trauma, however, this early-treatment approach may be effective as secondary prevention.

The Lancet Psychiatry

Volume 4, Issue 8

Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD); a double-blind, randomised, placebo-controlled, phase 3 trial

Anderson, et al.

This 12 week, multicenter phase 3 trial aimed to assess the efficacy, safety, and tolerability of fixed doses of novel vesicular monoamine transporter-2 inhibitor (VMAT-2), deutetrabenazine, for tardive dyskinesia. The researchers randomly assigned 298 patients with tardive dyskinesia to receive one of three fixed doses of deutetrabenazine (12 mg/day (n=75), 24 mg/day (n=74), or 36 mg/day (n=75)) or placebo (n=58). Compared with a change of -1.4 points (SE 0.41) in placebo group, the least-squares mean AIMS score improved by -3.3 points (0.42) in the deutetrabenazine 36 mg/day group, -3.2 points (0.45) in 24 mg/day group, and -2.1 points (0.41) in the 12mg/day group, with a treatment differences of -1.9 points (SE 0.58, 95% CI -3.09 to -0.79; p=0.001), -1.8 points (0.60, -3.00 to -0.63; p=0.003), and -0.7 points (0.57, -1.84 to 0.42; p=0.217), respectively, versus -1.4 points (0.41) in the placebo group. The proportion of patients with improvement of 50% or more in AIMS total score was greater in the deutetrabenazine 24 mg/day (35%; [OR] 3.96, 95% CI 1.46-10.72; p=0.005) and 36 mg/day (33%; 3.80, 1.40-10.36, p=0.007) groups than in the placebo group (47%). The frequency of adverse events was similar between patients in the deutetrabenazine groups (44-51%) and those in the placebo group (47%). Rates of depression and suicidality were similar to those with placebo.

Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: the multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial

Pagsbers, et al.

This multicenter, double-blind, randomized trial compared the efficacy and safety of quetiapine-extended release (quetiapine-ER) versus aripiprazole in children and adolescents with first-episode psychosis. A total of 113 patients from seven Danish university clinics were randomly assigned to 12 weeks of quetiapine-ER (target dose 600 mg daily) or aripiprazole (target dose 20 mg daily). Positive and Negative Syndrome Scale (PANSS) positive scores had a significant reduction of about 5-6 points in both groups (p<0.0001), but the drugs did not differ with regard to symptom reduction. Weight gain was more rapid with quetiapine-ER (p=0.0008), with an adjusted mean weight group difference at week 12

of 3.33 kg (SD 7.23; effect size 0.64; $p < 0.0001$). Akathisia was more common with aripiprazole at week 2 but not at other time points. Patients receiving aripiprazole reported more sedation. Notably, only 22 (23%) of patients experienced treatment response, defined as PANSS total score reduction of at least 30% plus Clinical Global Impressions-Improvement score of 1 (very much improved) or 2 (much improved). Additionally, 111 (98%) of patients experienced adverse reactions. In addition to sedation and akathisia, the most common adverse events were tremor, (79% in the quetiapine group vs 91% in the aripiprazole group), increased sleep duration (92% vs 71%), orthostatic dizziness (78% vs 81%), depression (80% vs 77%), failing memory (76% vs 77%) and weight gain (87% vs 68%).

Poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis: a prospective analysis.

Schoeler, et al.

Cannabis use following the onset of first-episode psychosis has been linked to both increased risk of relapse and non-adherence with antipsychotic medication. Authors investigated a group of 245 patients, obtaining retrospective data on active cannabis use and medication adherence shortly after first-episode psychosis, as well as risk of relapse at 2-year follow-up. Relapse was noted in 37% of patients. Continued cannabis use predicted poor outcome, including risk of relapse, number of relapses, length of relapse, and care intensity at follow up. In controlled equation modelling analyses, medication adherence partly mediated the effect of continued cannabis use on outcome, including risk of relapse (proportion mediated=26%), number of relapses (36%), time to relapse (28%) and care intensity (20%) but not length of relapse. Thus, between 20% and 36% of the adverse effects of continued cannabis used on outcome in psychosis might be mediated through the effects of cannabis use on medication adherence.

Journal of the American Academy of Child and Adolescent Psychiatry
Volume 56, Issue 8

Childhood Predictors of Adult Functional Outcomes in the Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder (MTA)

Roy, et al.

This study used data from the Multimodal Treatment of Children with ADHD (MTA), a 14-month randomized study of 579 children aged 7-10 with ADHD vs. a normative comparison group (n=258) with incremental follow-up into adulthood (mean age: 25), to determine effects of childhood demographics, clinical, and family factors on functional outcomes in adults with ADHD. Household income, IQ, and ADHD symptom severity influenced educational, emotional, occupational, sexual behavior, and police involvement outcomes. Parental factors influenced education. Psychiatric comorbidity affected income and emotional lability. Unexpected associations were higher IQ with increased number of jobs, nurturing parent style and more sexual partners, and higher baseline IQ with higher risk of mood disorders.

Sex Differences in the Relationship Between Conduct Disorder and Cortical Structure in Adolescents Smaragdi, et al.

This study sought to determine if brain cortical thickness (CT), surface area (SA), and local gyrification index (LGI) differed between male and female adolescents with conduct disorder (CD). MRI surface-based morphometry data from 48 males and 48 females ages 14-18 with CD in a European multisite study were compared to matched controls. Exclusion criteria were IQ <70, neurological disorder, TBI, ASD, and psychosis. Significant sex-by-diagnosis interactions included lower (male) and higher (female) supramarginal gyrus CT and higher (male) and lower (female) LGI and SA of the superior frontal gyrus relative to sex-matched controls. LGI and SA in the fusiform gyrus differed between males and females with CD. Contrary to previous data, there was no decrease in amygdala or striatal volume and greater SA was noted in CD participants relative to controls.

Concomitant Use of Atypical Antipsychotics With Other Psychotropic Medication Classes and the Risk of Type 2 Diabetes Mellitus

Burcu, et al.

This retrospective cohort study assessed the association between co-administration of atypical antipsychotics (AAP) with antidepressants or stimulants and risk of incident T2DM. All data were from Medicaid claims of youth 5-20 years old in four states between 2004-2009. A total of 73,224 youth were identified as new-users of AAP, 43.0% and 43.8% of which had concomitant antidepressant and stimulant use, respectively. Incidence of T2DM excluded youth with PCOS, type 1 diabetes, or antidiabetic medication use in absence of diagnosis. Data showed increased risk of incident T2DM with concomitant use of AAP and SSRI/SNRIs (RR=1.84) and TCAs (RR=2.75); other antidepressants and stimulants showed no increased risk. Risk increased with >180 days of exposure and higher cumulative dose.

Establishing Clinical Cutoffs for Response and Remission on the Screen for Child Anxiety Related Emotional Disorders (SCARED)

Caporino, et al.

The authors of this study investigated percentage of symptom reduction and raw score cutoffs on the SCARED-Parent (SP) and SCARED-Youth (SY) questionnaires to predict treatment response in youth with anxiety disorders. Data came from 438 youth with a primary anxiety disorder enrolled in the Child/Adolescent Anxiety Multimodal Treatment Study and a respective parent recruit. CGI score reduction to 1 or 2 determined response. 55% and 60% SP and 50% and 60% SY symptom reduction optimally predicted treatment response and remission, respectively, and 10 (SP) and 12 (SY) raw post-treatment scores predicted remission. SP scores demonstrated greater quality of efficiency. Limitations included a primarily non-Hispanic, white sample and elimination of youth with co-principle diagnoses.