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Research Watch is an initiative by the residents of University Hospitals Case Medical Center/ Case Western Reserve University, and 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)
- \* The International Journal of Psychoanalysis
- \* Journal of Child and Adolescent Psychopharmacology (JCAP)
- \* Neurology

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**Highlights**

- Perceived stress during pregnancy is associated with altered DNA methylation of placental glucocorticoid-pathway genes implying epigenetic regulation as a potential mechanism for psychopathology. (AJP)
- Youths with bipolar disorder and disruptive mood dysregulation disorder show similar levels of irritability but have distinct neural correlates when studied using face emotion labeling paradigm. (AJP)
- 16-year follow-up of borderline personality disorder reveals that the acute symptoms (such as self-harm) are more likely to remit and less likely to recur compared to temperamental symptoms. (AJP)
- Meta-analysis reveals 23% reduction in involuntary psychiatric admissions with the implementation of advance statements (eg, advance directives and crisis plans), while other interventions such as community treatment orders showed no reduction. (JAMA-P)
- Citalopram is not efficacious for complicated grief; it does show benefit for co-occurring depressive symptoms but only when combined with complicated grief psychotherapy treatment. (JAMA-P)
- In a longitudinal study of US Army Soldiers, 40% of soldiers who were enlisted but never deployed accounted for 61% of suicide attempts. (JAMA-P)
- SSRIs may be associated with an increased risk of acute angle-closure glaucoma. (JCP)
- A symptom trajectory with increasing depressive symptoms in the elderly may be a prodrome in the development of dementia. (LP)
- Meta-analysis shows that the initial mood episode of bipolar disorder is characterized by a prolonged prodrome lasting  $27.1 \pm 23.1$  months. (JAACAP)
- Case series describes the efficacy and initiation of long-acting injectable antipsychotics in adolescents, highlighting their under-utilization in this population. (JCAP)
- Children with APOE  $\epsilon 4\epsilon 4$  and  $\epsilon 2\epsilon 4$  genotypes appear to have smaller hippocampi and poorer cognitive performance. (Neurology)

## **The American Journal of Psychiatry**

### **Volume 173, Issue 7**

#### **Toward the Definition of a Bipolar Prodrome: Dimensional Predictors of Bipolar Spectrum Disorders in At-Risk Youths**

Hafeman, et al.

This study showed that offspring of parents with Bipolar I and II disorder demonstrated higher baseline levels of anxiety/depression, inattention/disinhibition, externalizing, subsyndromal mania and affective lability symptoms; the presence of the symptoms predicted the development of Bipolar I/II disorder. The strongest predictors were presence of anxiety/depression, affective lability and mania. Youths without these predictors had a 2% chance of converting to a bipolar spectrum disorder whereas those with all risk factors had a 49% predicted chance of conversion.

#### **Distress During Pregnancy: Epigenetic Regulation of Placenta Glucocorticoid-Related Genes and Fetal Neurobehavior**

Monk, et al.

This study investigated the effects of maternal distress on the fetus and epigenetic changes in placental genes because epigenetic regulation of placental glucocorticoid-pathway genes could be a potential mechanism for increased risk of psychopathology. Results showed while salivary cortisol levels were not associated with altered DNA methylation of placental glucocorticoid-pathway genes in placentas, perceived stress (measured by the Perceived Stress Scale) did affect change in DNA methylation, and was associated with greater DNA methylation.

#### **Neural Correlates of Irritability in Disruptive Mood Dysregulation and Bipolar Disorders**

Wiggins, et al.

The authors of this study used a face emotion labeling paradigm to examine the neural mechanisms behind irritability in DMDD and Bipolar Disorder in youths. Results demonstrated that irritability correlated with amygdala activity across all emotions in the DMDD group, whereas this was only present for fearful faces in the Bipolar group. Additionally, associations between neural activity and irritability in the ventral visual stream were found more consistently in the DMDD group than in the Bipolar Disorder group, especially in response to ambiguous angry faces. This suggests that due to distinct neural correlates, different approaches to treating irritability in the two disorders need to be considered.

#### **Fluidity of the Subsyndromal Phenomenology of Borderline Personality Disorder Over 16 Years of Prospective Follow-Up**

Zanarini, et al.

This work was an extension of the McLean Study of Adult Development studying the remissions and recurrences of symptoms of borderline personality disorder over 16 years of prospective follow-up. In the study acute symptoms (e.g., self-mutilation, help-seeking suicide attempts) of borderline personality disorder were more likely to remit for a period of 2 years and for a period of 4 years than the temperamental symptoms (e.g., chronic anger/frequent angry acts, intolerance of aloneness). These acute symptoms were also less likely to recur after a period of remission.

### **Interpersonal Psychotherapy for Mental Health Problems: A Comprehensive Meta-Analysis**

Cuijpers, et al.

This meta-analysis of randomized trials examined the effects of IPT and concluded that IPT is effective in the acute treatment of depression and even more effective when used in combination with pharmacological intervention. IPT is also effective in preventing the onset of new depressive disorders and reducing relapse. Evidence also suggests IPT's efficacy in the treatment of eating disorders and anxiety disorders.

### **JAMA Psychiatry**

### **Volume 73, Issue 7**

### **Interventions to Reduce Compulsory Psychiatric Admissions: A Systematic Review and Meta-analysis**

de Jong, et al.

This meta-analysis composing 2970 psychiatric patients showed a 23% statistically significant reduction in compulsory admissions (admissions against the will of the patient) if advance statements (eg, advance directives and crisis plans) were put in place. The presence of community treatment orders, compliance enhancement, and integrated treatment showed no such evidence reduction in compulsory psychiatric admissions.

### **Nature of Glutamate Alterations in Schizophrenia: A Meta-analysis of Proton Magnetic Resonance Spectroscopy Studies**

Merritt, et al.

Schizophrenia is associated with elevations in glutamatergic metabolites in the basal ganglia, thalamus and medial temporal lobe. No regions in the brain showed a decrease in glutamatergic metabolites. A meta-regression did not find support for the hypothesis that glutamatergic metabolite concentrations in patients vary in association with age, antipsychotic treatment, or symptom severity.

### **Efficacy and Safety of Basimglurant as Adjunctive Therapy for Major Depression: A Randomized Clinical Trial**

Quiroz, et al.

This RCT evaluated the safety and efficacy of basimglurant modified-release (MR) vs placebo as adjunctive therapy to ongoing antidepressant medication therapy in patients with MDD who had inadequate response within the current episode. Basimglurant works as an antagonist of the postsynaptic metabotropic glutamate subtype 5 receptor. There was no effect of the addition of basimglurant on primary outcomes but it did show improvement in patient-rated measures.

### **Optimizing Treatment of Complicated Grief: A Randomized Clinical Trial**

Shear, et al.

This is the first known placebo-controlled randomized clinical trial to evaluate the efficacy of antidepressant pharmacotherapy (citalopram), with and without complicated grief psychotherapy, in the treatment of complicated grief. It showed that complicated grief treatment (CGT) was superior to placebo alone in reducing outcome ( $p=.002$ ), and the addition of citalopram to complicated grief treatment did not further improve the complicated grief outcome ( $p=.84$ ). The addition of citalopram to CGT decreased depressive symptoms as measured by Quick Inventory of Depressive Symptoms, but showed no improvement in the absence of CGT.

### **Attention-Deficit/Hyperactivity Disorder Trajectories From Childhood to Young Adulthood: Evidence From a Birth Cohort Supporting a Late-Onset Syndrome**

Caye, et al.

This population based longitudinal study investigated whether impaired young adults with ADHD symptoms always have a childhood-onset disorder. ADHD was first screened for at age 11 years and then at ages 18 to 19 years and the rates of impairment in these two groups were compared to a control. Results showed that at age 11, 8.9% of individuals had ADHD and had a male predominance at 63.9%. In the young adult group, 12.2% had ADHD (with comorbidities), but there was a female predominance. Both groups had increased levels of impairment in adulthood, however, only 17.2% of children with ADHD continued to have it as young adults and only 12.6% of young adults had ADHD during childhood. This suggests the existence of 2 ADHD syndromes that have distinct developmental trajectories.

### **Evaluation of the Persistence, Remission, and Emergence of Attention-Deficit/Hyperactivity Disorder in Young Adulthood**

Agnew-Blais, et al.

Study examined ADHD and associated impairment, overall functioning, and other mental health disorders in the Environmental Risk Longitudinal Twin Study (England and Wales). Out of 2232 participants, 21.9% of children with ADHD (247 individuals) met criteria for the disorder at age 18 years. The persistence of the disorder was associated with more symptoms (OR 1.11) and a lower IQ (OR 0.98). By age 18 years, individuals with persistent ADHD had more functional impairment, including in school/work and friends/home life. They were more likely to have generalized anxiety disorder (OR 5.19), conduct disorder (OR 2.03), and cannabis dependence (OR 2.88). Individuals with late-onset ADHD showed fewer externalizing problems and higher IQ.

### **Risk Factors, Methods, and Timing of Suicide Attempts Among US Army Soldiers**

Ursano, et al.

This was a longitudinal retrospective cohort study of active duty soldiers from 2004-2009 to examine the suicide attempt risk factors, methods, and timing of attempt. All data was obtained from administrative and medical records. Of the 9650 soldiers who attempted suicide, most were males (86.3%) and younger than age 30 years (68.4%). Interestingly, 40% of soldiers who were enlisted but never deployed accounted for 61% of attempts, with highest risk being in the second month of service for never deployed for this group. Highest risk was in the sixth month of deployment for those on their first deployment. For those previously deployed, risk was highest at 5 months after return. Currently and previously deployed soldiers were more likely to attempt suicide with a firearm than those never deployed. Suicide attempts were more likely among soldiers who were women, in their first 2 years of service, and had a recently received a mental health diagnosis in the previous month. Among soldiers with 1 previous deployment, odds of a suicide attempt were higher for those who screened positive for depression or posttraumatic stress disorder after return from deployment and particularly at follow-up screening, about 4 to 6 months after deployment.

### **The Journal of Clinical Psychiatry**

#### **Volume 3, Issue 6**

### **The McLean-Harvard First-Episode Project: Early Course in 114 Cases of First-Episode Nonaffective Psychoses**

Tohen, et al.

This article aims to define the early course in nonaffective psychotic disorders other than schizophrenia. The authors followed 114 patients that were hospitalized for first episode nonaffective psychotic illness for > 2 years using various scales. Three-quarters of these patients achieved recovery within 2 years, with only 41% returning to baseline functioning, and half having a new episode of psychosis. The majority of these patients had a changed diagnosis in the end, indicating instability in DSM diagnoses.

### **Association of Selective Serotonin Reuptake Inhibitor Use and Acute Angle-Closure Glaucoma**

Chen, et al.

This article studies the relationship between SSRIs and the risk of acute angle-closure glaucoma (AACG) in the ethnic Chinese population in Taiwan, using a database for the period of 2000-2011, and recruiting 1,465 patients with newly diagnosed AACG and 5,712 people without AACG as controls. The adjusted odds ratio of AACG was 5.80 for patients who were on SSRIs within 7 days before the diagnosis of AACG, compared with non-users (95% CI, 1.89-17.9). This risk was higher with higher doses of SSRIs.

## **Efficacy for Psychopathology and Body Weight and Safety of Topiramate-Antipsychotic Cotreatment in Patients With Schizophrenia Spectrum Disorders: Results From a Meta-Analysis of Randomized Controlled Trials**

Correll, et al.

The authors did a meta-analysis of the efficacy and tolerability of topiramate-antipsychotic cotreatment in schizophrenia looking at 8 RCTs, with 439 patients randomized to topiramate (100-400mg/d) versus placebo. Topiramate-antipsychotic cotreatment reduced positive, negative, and general psychopathology as well as weight/BMI in patients with schizophrenia spectrum disorder, with larger studies needed to confirm and extend these findings.

### **The Lancet Psychiatry**

#### **Volume 3, Issue 7**

#### **10-Year Trajectories of Depressive symptoms and risk of dementia: A population based study**

Mirza, et al.

This population based study included cohort adults aged 55 years or older in Rotterdam (Netherlands) who were free from Dementia, but had data for depressive symptoms from at least one examination. The data was used to identify 10-year trajectories of depressive symptoms by latent class trajectory modelling. The participants were screened for dementia and followed up for 10 years for incident dementia. 5 trajectories of depressive symptoms were identified. The trajectory with increasing depressive symptoms was associated with a higher risk of dementia compared with low depressive symptom trajectory (HR 1.42, 95% CI 1.05-1.94;  $p=0.024$ ). This association remained even when analyses were repeated censoring for incident stroke, restricting to Alzheimer's disease as an outcome, and accounting for mortality as a competing risk for dementia. The higher risk of dementia only in the increasing trajectory suggests depression as a prodrome of dementia.

#### **Psilocybin with psychological support for treatment-resistant depression: an open label feasibility study**

Carhart-Harris, et al.

In this open-label feasibility trial, aimed to investigate feasibility, safety and efficacy of psilocybin in patients with unipolar treatment resistant depression, 12 patients (6 males and 6 females) with moderate to severe unipolar treatment-resistant major depression received two oral dosages of psilocybin (10mg and 25mg, 7 days apart) in supervised setting. There was no control group. The study found that relative to baseline, depressive symptoms were markedly reduced 1 week (mean QIDS difference -11.8, 95% CI -9.15 to -14.3,  $p=0.002$ , Hedges'  $g=3.11$ ) and 3 months (-9.2, 95% CI -5.69 to -12.71,  $p=0.003$ , Hedges'  $g=2$ ) after high dose treatment. There were marked improvements in anxiety and anhedonia.

**Journal of the American Academy of Child and Adolescent Psychiatry**  
**Volume 55, Issue 7**

**The Bipolar Prodrome: Meta-Analysis of Symptom Prevalence Prior to Initial or Recurrent Mood Episodes**

Van Meter, et al.

This study was a meta-analysis of prevalence of symptoms prior to an initial mood episode of bipolar disorder and the prevalence of subthreshold symptoms before a BD mood episode recurrence. Eleven studies demonstrated a prodromal period of approximately  $27.1 \pm 23.1$  months. In contrast, the period of subthreshold symptoms before the recurrent mood episodes was short, lasting  $1.0 \pm 0.9$  months. Symptoms were consistent with diagnostic criteria associated with mood polarity for both the initial prodrome and the period prior to a recurrent mood episode.

**The Effect of Exercise on Depressive Symptoms in Adolescents: A Systematic Review and Meta-Analysis**

Carter, et al.

This systematic review examined the treatment effect of physical exercise on depressive symptoms for adolescents aged 13 to 17 years. Eight trials were identified that provided necessary data for calculation of standardized effect size. Exercise did show a statistically significant moderate overall effect on depressive symptom reduction. Trials with exclusive clinical samples also showed a statistically significant moderate effect on depressive symptoms. Results point to exercise serving as a useful treatment strategy for depression.

**Effect of Parent Training on Adaptive Behavior in Children With Autism Spectrum Disorder and Disruptive Behavior: Results of a Randomized Trial**

Scahill, et al.

This 24-week, 6-site, randomized trial of parent training versus parent education in 180 children with autism spectrum disorder examined impact of parent training on adaptive behavior. Training consisted of specific strategies to manage disruptive behavior over 11 to 13 sessions, 2 telephone boosters, and 2 home visits. At week 24, the parent-training group showed a 5.7 point improvement from baseline on the Daily Living domain compared to no change in parent education. Improvement was also seen in the socialization domain. Higher-functioning children achieved significant gains in daily living skills.

**The International Journal of Psychoanalysis**  
**Volume 97, Issue 2**

**The metaphorical, the metonymical and the psychotic aspects of obsessive symptomatology**

Amir D

Amir suggests and integration of Lacanian and object-relations perspectives in formulating obsessive symptomatology. This formulation identifies metaphorical, metonymical, and psychotic aspects of obsessive symptoms and considers each aspect's role in allowing a person to symbolize and subsequent implications for psychoanalytic work.

### **Experiential self-understanding**

Bell & Leite

Bell and Leite examine insight from clinical and contemporary philosophical perspectives. They posit that insight is not sufficiently accounted for by cognition or internal self-observation. Instead, they propose that it is an ongoing process of the 'Unfolding articulation of one's psychic life'. This proposition highlights experience as significant in three ways: the source from which understanding arises; that, because it is contemporary with the unfolding process, understanding and experience are contemporaneous; and experience/understanding exist in a dynamic relationship.

## **Miscellaneous**

### **Efficacy of Long-Acting Injectable Antipsychotics in Adolescents**

Pope S & Zarea S

*Journal of Child and Adolescent Psychopharmacology*. 2016, 26(4): 391-394. doi:10.1089/cap.2015.0091.

The case series, based on a 24-month retrospective chart review at an acute inpatient psychiatric unit for children & adolescents, included two females and seven males within the ages of 14–17 years. Five were treated with paliperidone palmitate, and the rest with risperidone, fluphenazine, and aripiprazole. Primary psychiatric diagnoses were schizophrenia in five cases, and schizoaffective disorder, bipolar affective disorder-type I, bipolar affective disorder-not otherwise specified, and mood disorder-not otherwise specified in one case each. Noncompliance was a consideration in all cases with frequent running away and severity of illness being additional considerations in one case each. All of the patients required community resources with injectable services. This case series highlights the under-utilization of this effective modality of treatment in this population.

### **Gray matter maturation and cognition in children with different APOE ε genotypes**

Chang, et al.

*Neurology*. Published online before print July 13, 2016, doi: <http://dx.doi.org/10.1212/WNL.0000000000002939>

This cross-sectional study aimed to determine whether children with the 6 different APOE ε genotypes show differences in gray matter maturation, particularly for those with ε4 and ε2 alleles, which are associated with poorer outcomes in many neurologic disorders. Age-related changes in brain structures and cognition varied depending on genotype, with the smallest hippocampi in ε2ε4 children, and the lowest hippocampal fractional anisotropy in younger ε4ε4 children. Younger ε4ε4 children had the lowest

scores on executive function and working memory, while younger  $\epsilon 2\epsilon 4$  children performed worse on attention tasks. The  $\epsilon 4\epsilon 4$  and  $\epsilon 2\epsilon 4$  genotypes appear to negatively influence brain development in children.