

December 2016 - Volume 2, Issue 12

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Research Watch is an initiative by the residents of University Hospitals/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)
- \* Journal of the American Psychoanalytic Association
- \* Acta Psychiatrica Scandinavica
- \* Journal of Psychopharmacology

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**Highlights**

- Quetiapine monotherapy demonstrates efficacy in the treatment of PTSD in a 12-week RCT. (AJP)
- Preschool-age children with depression show a blunted response to rewards (JAACAP) and blunted neural response to rewards appears to be a prospective predictor of the development of depression in adolescent girls (AJP).
- A novel association is identified between loneliness and cortical amyloid burden in cognitively normal older adults, suggesting it as a neuropsychiatric symptom relevant to preclinical Alzheimer's disease. (JAMA-P)
- Randomized controlled trial suggests that N-acetylcysteine in combination with psychotherapy leads to improvement in PTSD symptoms, craving, and depression in subjects with co-occurring PTSD and SUD. (JCP)
- A case-cohort analysis suggests that psychostimulant and SNRI exposure following the 20th week of gestation conveys increased risk for the emergence of hypertensive disorders of pregnancy. (JCP)
- CRP concentrations are increased in bipolar disorder in all mood states, but are higher during mania than in depression and euthymia. (LP)
- Use of adjunctive second-generation antidepressants is associated with a small reduction in symptoms of acute bipolar depression, but there is no increase in clinical response or remission rates. (LP)
- In youth with bipolar disorder, there is a strong correlation between obesity and suicide attempts, hospitalization, abuse, and conduct disorder. (JAACAP)
- A registry-based study suggests a dose-response relationship between treatment of bacterial infections and subsequent onset of schizophrenia and affective disorders. (Acta Psychiatrica Scandinavica)
- In two small placebo-controlled, crossover trials, a single large dose of psilocybin showed benefits for patients suffering from cancer-related depression and anxiety for up to six months. (Journal of Psychopharmacology)

## **The American Journal of Psychiatry**

### **Volume 173, Issue 12**

#### **Early Improvement in Work Productivity Predicts Future Clinical Course in Depressed Outpatients: Findings From the CO-MED Trial**

Jha, et al.

Authors analyzed trajectories of change in work productivity (measured by the Work Productivity and Activity Impairment self-report questionnaire) in 331 subjects during the first 6 weeks of treatment, and investigated if it could be used to predict remission at 3 and 7 months. Three distinct trajectories of changes in work productivity were identified: 1) robust early improvement (24%), 2) minimal change (49%), and 3) high-impairment slight reduction (27%). Those with robust improvement had 3–5 times higher remission rates at 3 months and 2–5 times higher remission rates at 7 months compared to others, even after controlling for other variables.

#### **Efficacy of Quetiapine Monotherapy in Posttraumatic Stress Disorder: A Randomized, Placebo-Controlled Trial**

Villarreal, et al.

This was a 12-week randomized, placebo-controlled trial to assess the efficacy of quetiapine monotherapy in the treatment of posttraumatic stress disorder (PTSD). Average dose of quetiapine used was 258 mg (range, 50–800 mg). Reductions in Clinician-Administered PTSD Scale (CAPS) total, re-experiencing, and hyperarousal scores were significantly greater for the quetiapine group than for the placebo group. There were also significant improvements in secondary measures such as the Davidson Trauma Scale, HAM-D and HAM-A. Adverse events were generally mild and expected based on prior studies of quetiapine in this and other patient population.

#### **Blunted Neural Response to Rewards as a Prospective Predictor of the Development of Depression in Adolescent Girls**

Nelson, et al.

The authors examined whether the reward positivity prospectively predicted the development of depression 18 months later in a large community sample of adolescent girls. In a sample of 444 girls, a blunted reward positivity at baseline predicted first-onset depressive disorder and greater depressive symptom scores 18 months later. The combination of a blunted reward positivity and greater depressive symptom scores at baseline provided the greatest positive predictive value for first-onset depressive disorder.

**JAMA Psychiatry**  
**Volume 73, Issue 12**

**Disease Burden and Symptom Structure of Autism in Neurofibromatosis Type 1: A Study of the International NF1-ASD Consortium Team (INFACT)**

Morris, et al.

To assess the quantitative autistic trait (QAT) burden in individuals with neurofibromatosis type 1 (NF1), researchers analyzed anonymized, individual-level primary data from six tertiary referral centers in the United States, Belgium, United Kingdom and Australia. Among 531 individuals included in the study, QAT scores were continuously distributed and pathologically shifted with 13.2% scoring in the severe range, wherein the male to female ratio was attenuated (1.6:1) compared to idiopathic ASD. Within-family correlation for QAT burden was greater among individuals with NF1-affected first degree relatives, as compared to the general population and families with ASD.

**Association of Genetic Risk Variants With Attention-Deficit/Hyperactivity Disorder Trajectories in the General Population**

Riglin, et al.

A prospective population-based cohort study evaluated whether genetic risk variant load for ADHD (indexed by polygenic risk scores) is associated with symptom trajectories across childhood and adolescence, and whether higher genetic liability for ADHD is correlated with childhood multimorbidity. Among 9757 children with data on ADHD symptoms, four symptom trajectories were identified: low, intermediate, childhood-limited, and persistent. Mean polygenic risk scores were higher for children in the persistent trajectory (0.254) compared with each of the other trajectory groups (low, -0.018; intermediate 0.054; and childhood-limited, 0.017). The proportion of children with additional neurodevelopmental disorders was also highest in the persistent trajectory group at 42.5%.

**Sex-Specific Alterations of White Matter Developmental Trajectories in Infants With Prenatal Exposure to Methamphetamine and Tobacco**

Chang, et al.

A case-control study showed of 139 neonates showed that all infants exposed prenatally to methamphetamine and tobacco showed delayed developmental trajectories on active muscle tone ( $P < .001$ ) and total neurologic scores ( $P = .01$ ) that normalized by ages 3 to 4 months. Sex specific differences were identified with methamphetamine/tobacco-exposed boys having significantly delayed trajectories in superior and posterior corona radiata that normalized by ages 3 to 4 months. Methamphetamine/tobacco-exposed girls showed persistently lower fractional anisotropy in anterior corona radiata. All tobacco-exposed infants showed persistently lower axial diffusion in the thalamus and internal capsule across groups ( $P = .02$ ) suggesting aberrant axonal development.

### **Association of Higher Cortical Amyloid Burden With Loneliness in Cognitively Normal Older Adults**

Donovan, et al.

This cross-sectional study of 79 community-dwelling older adults aimed to determine whether cortical amyloid burden (an in vivo research biomarker of Alzheimer's Disease) is associated with greater loneliness in cognitively normal older adults. Results showed that higher brain amyloid burden was associated with more frequent feelings of isolation, being left out, and lacking companionship, independent of sociodemographic factors, objective measures of social network, depressive and anxiety symptoms.

### **Cognitive Subtypes of Schizophrenia Characterized by Differential Brain Volumetric Reductions and Cognitive Decline**

Weinberg, et al.

In this study of 96 patients with schizophrenia, cluster analytical techniques revealed 4 IQ-based subgroups in which all those assessed had significantly reduced inferior parietal volume relative to healthy controls ( $P < .001$ ). However, there was also a severely deteriorated group with significantly reduced total hippocampal ( $P = .01$ ), lingual gyrus ( $P = .05$ ), and superior temporal sulcus ( $P = .05$ ) gray matter volumes relative to the preserved group.

## **The Journal of Clinical Psychiatry**

### **Volume 3, Issue 11**

#### **A Double-Blind, Randomized, Controlled Pilot Trial of N-Acetylcysteine in Veterans with Posttraumatic Stress Disorder and Substance Use Disorders**

Back, et al.

This double-blind randomized controlled trial of 35 veterans with co-occurring posttraumatic stress disorder (PTSD) and substance use disorders (SUDs) studied the efficacy of N-acetylcysteine in combination with psychotherapy in treating these disorders which are known to effect glutamate synapses in the nucleus accumbens. Participants were randomly assigned to an 8-week course of course of N-acetylcysteine (2,400 mg/d) or placebo in addition to cognitive-behavioral therapy for SUD. Those treated with N-acetylcysteine showed significant improvements in PTSD symptoms, cravings, and depression ( $\beta$  values  $< -0.33$ ;  $P$  values  $< .05$ ). There were no significant between-group differences in the outcome of substance use, as it was low for both groups.

#### **Effectiveness of Antipsychotic Drugs for 24-Month Maintenance Treatment in First-Episode Schizophrenia: Evidence From a Community-Based "Real-World" Study**

Zhang, et al.

This study investigated the effectiveness of various antipsychotic medications over a prospective 24-month maintenance period following first-episode schizophrenia. A total of 312 participants from 2 community settings completed the 24-month follow-up, who were divided into 7 groups based off medication used: aripiprazole, clozapine, chlorpromazine, olanzapine, perphenazine, quetiapine, and risperidone. Symptoms were assessed from various scales including the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I). The Personal and Social Performance scale (PSP) was used to evaluate the patients' social functioning. The Medication Adherence Rating Scale (MARS) was used to assess medication adherence behavior. Between the different medication groups, no significant differences were observed among the 7 studied medication groups in PANSS, CGI-S, CGI-I, PSP, and MARS scores. Remission rates increased as follow-time lapsed. The authors concluded that the antipsychotic medications studied achieved equivalent effectiveness in maintenance treatment of first-episode schizophrenia with the guidance of a well-organized case management program and family participation.

### **Effect of Aripiprazole Lauroxil on Metabolic and Endocrine Profiles and Related Safety Considerations Among Patients with Acute Schizophrenia**

Nasrallah, et al.

The authors performed a secondary analysis of the effects of the long-acting injectable antipsychotic, aripiprazole lauroxil on body weight, fasting blood and serum lipids, glycosylated hemoglobin (HbA1c), prolactin, and treatment-emergent adverse events in patients with Schizophrenia over 12 weeks. A total of 622 participants were randomized into three different groups receiving monthly intramuscular injections of aripiprazole lauroxil 441mg, aripiprazole lauroxil 882mg, or placebo. No clinical relevant changes were observed in serum lipids, lipoproteins, plasma glucose, or HbA1c among the groups over the 12 weeks. Those receiving aripiprazole lauroxil were found to have a reduction in mean prolactin levels, whereas the placebo group did not. These results indicated that aripiprazole lauroxil is well tolerated, with a relatively low-risk metabolic profile compared to other antipsychotics.

### **Prenatal Psychostimulant and Antidepressant Exposure and Risk of Hypertensive Disorders of Pregnancy**

Newport, et al.

A case-cohort analysis was conducted of 686 pregnant women enrolled in a prospective, longitudinal observational study. Hypertensive Disorders of Pregnancy were significantly associated with psychostimulants (OR 6.11) and SNRIs (OR 2.57) when exposed following the 20th week of gestation. There was also an association with cocaine dependence (OR 2.99) and panic disorder (OR 1.78), but no other psychiatric illnesses were associated with an increased risk of hypertension during pregnancy. The risk was highest for higher maternal daily doses of amphetamine psychostimulants and venlafaxine. There was no association with SSRIs, mood stabilizers, or antipsychotics.

### **Trajectories of Perinatal Depressive and Anxiety Symptoms in a Community Cohort**

Bayrampour, et al.

A community cohort study from Alberta, Canada looked at anxiety and depressive symptoms during second and third trimesters as well as 4 and 12 months postpartum. Five distinct trajectory groups were identified: minimal, mild, antepartum, postpartum, and chronic. Common risk factors for both depression and anxiety included: mental health issues (OR 1.83-7.64), history of abuse/neglect (OR 1.67-8.97), and low social support (OR 1.64-11.37). The magnitude of the influence of the psychosocial risk factors was greater in the chronic group (2.4% of the participants fell into this category). Distinct risk factors for the chronic depression group included being single and younger maternal age. Women with antepartum depression and anxiety were more likely to be new immigrants or have an infertility history.

## **The Lancet Psychiatry**

### **Volume 3, Issue 12**

#### **C-reactive protein concentration across the mood spectrum in bipolar disorder: a systematic review and meta-analysis**

Fernandes, et al.

This systematic review and meta-analysis aimed to investigate whether peripheral concentrations of C-reactive protein (CRP), an acute-phase response protein of inflammatory activity, are increased in bipolar disorder across the mood spectrum. Using data from 27 studies, author report that compared with healthy individuals, CRP concentrations were moderately increased in people with bipolar disorder during depression and euthymia and more substantially increased during mania. The extent of increase in CRP concentrations in mania and depression was not related to symptoms severity. CRP concentrations were moderately decreased after resolution of an index manic episode and slightly decreased after resolution of an index depressive episode.

#### **Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabilizer or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomized placebo-controlled trials**

McGirr, et al.

This systematic review and meta-analysis aimed to study the efficacy and safety of second-generation antidepressants in treating acute bipolar depression. Randomized, double-blind, placebo-controlled trials of second generation antidepressants adjunctive to a mood stabilizer or an antipsychotic in patients with acute bipolar depression were included. Authors identified six trials representing 1383 patients with bipolar depression. Second-generation antidepressants were associated with a small but significant improvement in clinician-rated depressive symptom score. However, clinical response and remission rates did not differ significantly between patients receiving adjunctive antidepressants and those receiving placebo for clinical response. Acute treatment was not associated with an increased risk of treatment-emergent mania or hypomania, but 52-week extension periods were associated with an increase risk.

**Journal of the American Academy of Child and Adolescent Psychiatry**  
**Volume 55, Issue 12**

**Correlates of Overweight and Obesity Among Adolescents With Bipolar Disorder in the National Comorbidity Survey-Adolescent Supplement**

Goldstein, et al.

This study examined for correlates of overweight and obesity in individuals with bipolar disorder using the National Comorbidity Survey-Adolescent supplement, a face-to-face survey of mental disorders from 2001 through 2004. The method involved utilizing a modified version of the fully structured World Health Organization Composite International Diagnostic Interview. Results indicated no significant differences in weight categories across groups (bipolar disorder group, major depressive disorder group, and control group without mood disorders). Overweight and obesity in adolescents with bipolar disorder correlated with significantly higher lifetime rates of suicide attempts, physical or sexual abuse, binge eating or bulimia, and conduct disorder.

**Comparing Brain Morphometry Across Multiple Childhood Psychiatric Disorders**

Gold, et al.

This study compared gray matter volume among youth with anxiety disorders, bipolar disorder, disruptive mood dysregulation disorder, attention-deficit/hyperactivity disorder, and healthy volunteers. T1-weighted magnetic resonance imaging scans were obtained in 184 youths. Youth with bipolar disorder, anxiety, and healthy volunteers all showed specific differences in the left dorsolateral prefrontal cortex. Gray matter volume was increased in youth with anxiety but decreased in bipolar disorder relative to healthy volunteers. Both bipolar disorder and disruptive mood dysregulation disorder showed decrease gray matter volume relative to healthy volunteers in the right dorsolateral prefrontal cortex/superior frontal gyrus.

**Longitudinal Course of Bipolar disorder in Youth With High-Functioning Autism Spectrum Disorder**

Borue, et al.

This study's aim was to provide the first longitudinal characterization of mood and psychosocial functioning in youth with comorbid bipolar and autism spectrum disorders. The Course and Outcome of Bipolar Youth study followed 368 youth with DSM-IV bipolar I, bipolar II or not otherwise specified for an average of 9 year. The analysis compared youth with and without ASD on clinical presentation, percentage of time with mood symptomology, and psychosocial functioning. Results indicated that youth with bipolar disorder plus autism spectrum disorder exhibit typical bipolar mood symptoms but with earlier onset, a mixed symptom presentation, and additional functional impairments. Presentations also more frequently involved distractibility, racing thoughts, depressed mood, and social withdrawal. The symptomatic differences were generally strongest early and decreased over time.

## **Neural Correlates of Reward Processing in Depressed and Healthy Preschool-Age Children**

Belden, et al.

This study's aim was to assess whether, similar to adults and adolescents, pre-school age kids with depression showed a blunted neural response to rewards. The study population was fifty-three 4-to-7 year old children with depression and 25 psychiatrically healthy children of the same age. The study required individuals to complete a simple guessing task in which points could be won or lost on each trial while event-related potentials were recorded. The children with depression showed a reduced differentiation between responses to gains and losses and also showed a blunted response to the reward, even when controlling for co-existing attention-deficit/hyperactivity disorder, oppositional defiant disorder, and generalized anxiety disorder.

## **Journal of the American Psychoanalytic Association**

### **Volume 64, Issue 5**

#### **Masochism and its Rhythm**

Civitarese G,

Civitarese begins by considering three Freudian texts regarding masochism: "A Child is Being Beaten," Beyond the Pleasure Principle, and "The Economic Problem of Masochism." Civiterese focuses on rhythm as a qualitative aspect of masochism and its role in precipitating pleasure from pain by dreaming a traumatic interaction as well as feeling it in the body.

#### **Finding Control Cases and Maintaining Immersion: Challenges and Opportunities**

Ehrlich LT

Ehrlich considers an old problem in psychoanalytic training: finding control cases. She suggests that it is by understanding candidates' internal challenges to finding cases that control cases will find candidates. She goes on to make recommendations for institutional solutions.

## **Acta Psychiatrica Scandinavica**

### **Infections and exposure to anti-infective agents and the risk of severe mental disorders: a nationwide study**

**Epub ahead of print, 2016 November 21**

Köhler, et al.

Using Danish national registry data from 1995 through 2013, the authors conducted the first large-scale, population based study on whether infectious diseases increase psychiatric risks. Of 1 015 447 individuals who submitted prescriptions for infectious-disease treatments, 5 760 subsequently had a first diagnosis or psychiatric contact for a schizophrenia spectrum disorder, and 13 044 for affective disorders

(depression or bipolar disorder). Risk for schizophrenia or affective disorders were increased 37% and 64%, respectively, for individuals redeeming any anti-infective prescription as compared to individuals who did not. Risks had dose-response relationships with the total number of prescriptions and number of different types of anti-infective agents. Among patients redeeming >20 prescriptions, the risk was even higher (HRR: schizophrenia, 1.68; affective disorders, 3.16). Excess risk for subsequent first psychiatric diagnosis was significant for infections treated with antibiotics (HRR for broad-spectrum antibiotics: schizophrenia, 1.53; affective disorders, 1.65) but not for antivirals, antimycotics, or antiparasitic agents. Patients hospitalized for infectious diseases were at a greater risk than those treated on an outpatient basis (HRR: schizophrenia, 2.05; affective disorders, 2.59).

## Journal of Psychopharmacology

### Volume 30, Issue 12

#### **Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial**

Ross, et al.

In a small double-blind, placebo-controlled, crossover trial, 29 patients with cancer-related anxiety and depression were treated for two sessions with single-dose psilocybin (0.3 mg/kg) or niacin control, both in conjunction with psychotherapy. Prior to crossover at 7 weeks, psilocybin produced significant differences between groups with the psilocybin group demonstrating immediate, substantial, and sustained clinical benefits according to each of six primary outcome measures (HADS T, HADS A, HADS B, BDI, STAI S, STAI T) evaluating reduction of anxiety and depression symptoms. At 6.5 month follow-up, psilocybin was associated with enduring anxiolytic and anti-depressant effects with 60-80% of participants demonstrating clinically significant reductions in depression or anxiety, as well as sustained benefit in existential distress, quality of life and attitudes towards death.

#### **Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial**

Griffiths, et al.

Another two-session, randomized, double-blind, crossover trial of 51 patients with life-threatening cancer diagnoses and symptoms of depression and/or anxiety was performed to evaluate the effects of very low "placebo-like" dose (1 or 3 mg/70 kg) versus high dose (22 or 30mg/70 kg) psilocybin with five weeks between sessions and 6-month follow-up. High-dose psilocybin produced large decreases in clinician-evaluated and self-reported measures of depressed mood and anxiety, increased quality of life, perceived life meaning, optimism, and decreased death anxiety. At 6-month follow-up, overall rate of clinical response was 78% for clinician-rated depression and 83% for anxiety. A high percentage of patients (80%) reported increased well-being and life satisfaction with high-dose treatment. Overall rate of symptom remission was reported to be 65% and 57%. No serious adverse events attributed to psilocybin administration occurred.