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Research Watch is an initiative by the residents of University Hospitals Case 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

### *Pregnancy & Psychiatry*

- Prenatal nicotine exposure appears to be associated with an increased risk of schizophrenia in the offspring. (AJP)
- Untreated depression is found to be associated with increased risks of preterm birth and low birth weight. (JAMA-P)
- Prenatal exposure to acute stress appears to be associated with depression in adolescent offsprings. (JAACAP)

### *Depression*

- A population study indicates that concomitant treatment with SSRIs and statins is associated with lower risk for psychiatric hospital contacts. (AJP)
- A randomized, double blind study suggests that whole body hyperthermia is a safe, rapid-acting treatment for major depression. (JAMA-P)

### *Schizophrenia*

- An  $\alpha 7$  nicotinic receptor partial agonist demonstrates a procognitive effects in nonsmoking subjects with schizophrenia. (AJP)
- Second-generation antipsychotics appear to be associated with higher quality of life compared to first-generation antipsychotics in schizophrenia. (LP)

### *Miscellaneous*

- Case reports describe catatonia in the context of clozapine withdrawal and Creutzfeldt-Jakob Disease. (JCP)
- After an episode of self-harm, cognitive-behavioral based therapy appears to be associated with fewer individuals repeating self-harm and dialectical behavior therapy appears to be associated with reduced frequency of self-harm. (LP)
- Combined stimulant and guanfacine treatment in ADHD appears to be clinically superior to monotherapy, especially for inattentive symptoms. (JAACAP)
- Functional imaging studies suggest that increased marijuana use is associated with altered reward anticipation. (JAMA-P)

## **The American Journal of Psychiatry**

### **Volume 173, Issue 8**

#### **Concurrent and Sustained Cumulative Effects of Adolescent Marijuana Use on Subclinical Psychotic Symptoms**

Bechtold, et al.

This longitudinal study followed 1,009 adolescent males and recorded their self-reported frequency of marijuana use, subclinical psychotic symptoms and several time-varying confounds on an annual basis. Results demonstrated that for every year of engaged marijuana use, the expected level of subsequent subclinical psychotic symptoms rose by 21% and the expected odds of experiencing subclinical paranoia or hallucinations rose by 133% and 92%, respectively. These effects persisted even after abstinence for 1 year.

#### **Prenatal Nicotine Exposure and Risk of Schizophrenia Among Offspring in a National Birth Cohort**

Niemela, et al.

This case-control study examined the relationship between prenatal nicotine exposure and schizophrenia by prospectively measuring maternal serum cotinine levels (metabolite of nicotine & biomarker of nicotine exposure) using quantitative immunoassays and identifying cases of schizophrenia in offspring from a national registry. Results showed higher maternal cotinine levels were associated with an increased odds of schizophrenia (odds ratio=3.41, 95% CI, 1.86-6.24) and categorically heavy maternal nicotine exposure was related to a 38% increased odds of schizophrenia. The study took into account confounders such as maternal age, parental psychiatric disorders, socioeconomic status as well as other covariates.

#### **The Effect of Concomitant Treatment with SSRIs and Statins: A Population-Based Study**

Kohler, et al.

A cohort study suggests concomitant use of SSRIs with statins results in better psychiatric outcomes compared to SSRI used alone. This nationwide cohort study from Denmark included all incident SSRI users between 1997 and 2012, and the investigators compared people who had periods of concomitant use of SSRIs and statins with people who had periods of SSRI treatment alone. Authors report that individuals using both an SSRI and a statin were associated with a significantly lower risk for psychiatric hospital contacts from any cause (adjusted hazard ratio=0.75, 95% CI=0.69, 0.82) and for psychiatric hospital contacts due to depression (adjusted hazard ratio=0.64, 95% CI= 0.55, 0.75.) The concomitant use of SSRIs and statins was not associated with significant increase in all-cause mortality or suicidal behavior.

#### **A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients with Treatment-Resistant Depression**

Singh, et al.

This multicenter, double-blind, placebo-controlled study demonstrated that twice-weekly and thrice-weekly administration of IV ketamine at 0.5mg/kg infused over 40 minutes (for a duration of 2 weeks, with an additional optional 2-week open label phase) maintained antidepressant efficacy over 15 days and both regimens were relatively well tolerated. Most common side effects included headache, anxiety, dissociation, nausea and dizziness (>20%.) Dissociative symptoms were transient and attenuated with repeated dosing.

### **A Randomized Trial to Assess the Efficacy and Safety of ABT-126, a Selective $\alpha 7$ Nicotinic Acetylcholine Receptor Agonist, in the Treatment of Cognitive Impairment in Schizophrenia**

Haig, et al.

This double-blind, placebo-controlled, parallel-group phase 2 study randomized 207 stable patients with schizophrenia to receive either once-daily dosing with 10mg of ABT-126, 25mg of ABT-126 or placebo. The primary measure was change from baseline to week 12 on the MATRICS Consensus Cognitive Battery composite score. Over-all results fell short of significance, however, the study found a significant difference between smoking and nonsmoking subjects and ABT-126 demonstrated a significant procognitive effect in verbal learning, working memory and attention in nonsmoking subjects. In general, ABT-126 was well tolerated and the most common side effects included diarrhea, dizziness and fatigue (all occurring in <8%.)

### **JAMA Psychiatry**

### **Volume 73, Issue 8**

### **Efficacy of Augmentation of Cognitive Behavior Therapy With Weight-Adjusted D-Cycloserine vs. Placebo in Pediatric Obsessive-Compulsive Disorder: A Randomized Clinical Trial**

Storch, et al.

This placebo-controlled RCT looked at the treatment of children with obsessive compulsive disorder (OCD) to determine if the addition of D-cycloserine, a partial agonist at the N-methyl-D-aspartate receptor in the amygdala, would provide any additive benefit to cognitive behavioral therapy. After 10 sessions of CBT, along with weight adjusted D-cycloserine in the intervention group, there was no difference between the groups in reduction of OCD symptoms on the Children's Yale-Brown Obsessive Compulsive Scale or the Clinical Global Impressions Scale.

### **Whole-Body Hyperthermia for the Treatment of Major Depressive Disorder: A Randomized Clinical Trial**

Janssen, et al.

A double-blind RCT evaluated the efficacy of a single episode of whole-body hyperthermia to 38.5°C versus a sham condition in the reduction of depressive symptoms. Participants were medically healthy, aged 18 to 65 years, met criteria for major depressive disorder, were free of psychotropic medication use, and had

a baseline 17-item Hamilton Depression Rating Scale score of 16 or greater. The intervention group showed a statistically significant decrease in HAM-D scores at weekly intervals over a 6-week period.

### **Triggers for Violent Criminality in Patients With Psychotic Disorders**

Sariaslan, et al.

A population-based time-stratified case-crossover study, showed that triggers, including exposure to violence, traumatic brain injuries, unintentional injuries, self-harm, substance intoxication, and parental bereavement, were associated with elevated relative risks of violent crime among patients with psychotic disorders in the week after their occurrence compared with earlier periods within the same individuals. The largest 1-week absolute risk of violent crime was observed following exposure to violence.

### **Structural and Functional Brain Abnormalities in Attention-Deficit/Hyperactivity Disorder and Obsessive-Compulsive Disorder: A Comparative Meta-analysis**

Norman, et al.

This meta-analysis revealed that ADHD and OCD have disorder-specific functional and structural abnormalities in the basal ganglia and insula, which were reduced in ADHD but increased in OCD relative to controls, and in frontal regions, where rostral-medial frontal regions were disorder-specifically decreased in structure and function in OCD but ventrolateral prefrontal regions were disorder-specifically underfunctioning in ADHD.

### **Neonatal Outcomes in Women with Untreated Antenatal Depression Compared With Women Without Depression: A Systematic Review and Meta-analysis**

Jarde, et al.

A systematic review and meta-analysis examined neonatal outcomes in women with depression receiving neither pharmacological nor non-pharmacological treatment as compared with women without depression. In the 23 observational studies meeting inclusion criteria, untreated depression was found to be associated with significantly increased risks of preterm births and low birth rate with a trend toward higher risks of exposure to more severe depression.

### **Association of Marijuana Use With Blunted Nucleus Accumbens Response to Reward Anticipation**

Martz, et al.

Young adult marijuana users were recruited from an ongoing longitudinal study of youths at high risk for substance use and underwent 3 consecutive MRIs over 3 years. Cross-lagged panel models were used to test the association of marijuana use with neural response in the nucleus accumbens (NAcc) to reward anticipation during a monetary incentive delay task. Greater marijuana use was associated with later blunted activation of the NAcc during reward anticipation. The authors concluded that, over time, marijuana may alter anticipatory reward processing which may increase the risk for continued drug use and later addiction.

### **Polygenic Risk of Psychosis and Ventral Striatal Activation During Reward Processing in Health Adolescents**

Lancaster, et al.

Researchers performed a cross-sectional study using data from the IMAGEN project (a European, multicenter, genetic-neuroimaging study of reinforcement sensitivity in adolescents) to assess whether common genetic risk alleles for psychosis influence response to rewarding stimuli in healthy adolescents. Results showed a positive association between polygenic risk profile score (RPS) for psychosis and blood oxygen level dependency (BOLD) in the ventral striatum during reward anticipation. Psychosis RPS was shown to be associated with reduced performance IQ. No association was observed between psychosis RPS and behavioral impulsivity.

### **Dopamine-Related Disruption of Functional Topography of Striatal Connections in Unmedicated Patients with Schizophrenia**

Horga, et al.

This multi-nodal, case-control study sought to examine whether the pattern of brain connectivity across striatal subregions is abnormal in unmedicated patients with schizophrenia and to determine whether this abnormality relates to psychotic symptoms. Study used resting-state functional MRI data from unmedicated patients with schizophrenia and healthy controls. Patients were found to have an abnormal pattern of striatal connectivity, which included abnormal caudate connections with a distributed set of associative cortex regions. Severity of positive symptoms correlated with degree of deviation from the multivariate pattern of striatal connectivity. Findings suggest that striatal-cortical dysconnectivity may underlie the effects of dopamine dysregulation as the pathophysiologic mechanism of psychotic symptoms.

## **The Journal of Clinical Psychiatry**

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

#### **Sudden-Onset Catatonia Following Clozapine Withdrawal: A Case Report**

Koychev, et al.

This case report describes a 22-year-old patient who was treated with Clozapine. The clozapine was stopped due to concerns of pericarditis. Pericarditis was ruled out, however the patient subsequently developed catatonic symptoms 4 days following cessation. Abruptly stopping Clozapine has been linked with risk of delirium, vomiting, dyskinesias, and catatonia. The withdrawal reactions may be due to muscarinic or dopaminergic rebound. Some believe anticholinergics and Olanzapine can help prevent the withdrawal. Clozapine can safely be reinstated following withdrawal reactions.

## **A Case of Creutzfeldt-Jakob Disease Presenting as Catatonia**

Winton, et al.

This case reports a 61-year-old man who presented with 2-week history of confusion, word-finding difficulties, slurred speech, and right-hand clumsiness. Neurology workup was unremarkable. There was further progression with symptom development of upper limb posturing and apraxia. Patient was diagnosed with atypical catatonia and treated with ECT. He continued to deteriorate, requiring a neuropsychiatric consult and diagnosed with Creutzfeldt-Jakob disease (CJD) based off clinical and imaging findings on the patient's previous MRI scan, and further testing including DWI MRI, EEG, CSF studies. The deterioration continued with more frequent myoclonic jerks and altered consciousness. Patient died 4 weeks later and autopsy confirmed the diagnosis of CJD. In summary, whenever a patient with catatonia-like symptoms has rapidly progressive deterioration of cognition with neurologic findings, CJD should be in the differential.

## **The Lancet Psychiatry**

### **Volume 3, Issue 8**

#### **Effects of First-Generation Antipsychotics versus Second-Generation antipsychotics on quality of life in schizophrenia: A double-blind, Randomized study**

Grunder, et al.

This multicenter, randomized, double-blinded neuroleptic strategy study (NeSSy) aimed to compare quality of life in patients with schizophrenia on First-Generation Antipsychotics (FGAs) versus Second-Generation Antipsychotics (SGAs). Double randomization allowed for restricted selection of a treatment within each antipsychotic drug group (FGA or SGA) for an individual patient. Haloperidol and flupentixol were available among FGAs and aripiprazole, olanzapine and quetiapine were available from SGAs. Subjects were randomly assigned to either treatment with FGAs or SGAs. Mean area under curve (AUC) values of SF-36 (measuring quality of life) were significantly higher in the SGA group than in the FGA group. Clinical Global Impression scores decreased in both groups, but were not significantly different. The increase in body-mass index (BMI) was significantly higher in the SGA group than in the FGA group.

#### **Psychosocial interventions following self-harm in adults: a systematic review and meta-analysis**

Hawton, et al.

This Cochrane systematic review & meta-analysis looked at randomized controlled trials of psychosocial interventions for adults after a recent (within 6 months) episode of self-harm. Cognitive-behavioral-based psychotherapy was associated with fewer participants repeating self-harm at 6 months' (odds ratio 0.54) and at 12 months' follow-up (0.80). Patients receiving dialectical behavior therapy (in three trials) were not less likely to repeat self-harm compared with those provided with treatment as usual at 6 months. However, the secondary endpoint of frequency of self-harm was associated with a significant reduction

with use of dialectical behavior therapy. Case management and sending regular postcards did not reduce repetition of self-harm.

### **Neurobiology of addiction: a neurocircuitry analysis**

Koob, et al.

This analysis discusses that the drug addiction represents a dramatic dysregulation of motivational circuits that is caused by a combination of exaggerated incentive salience and habit formation, reward deficits and stress surfeits, and compromised executive function in three stages. The study discusses that the rewarding effects of drugs of abuse, development of incentive salience, and development of drug-seeking habits in the binge/intoxication stage involve changes in dopamine and opioid peptides in the basal ganglia. Molecular genetic studies have identified transduction and transcription factors that act in neurocircuitry associated with the development and maintenance of addiction that might mediate initial vulnerability, maintenance, and relapse associated with addiction.

## **Journal of the American Academy of Child and Adolescent Psychiatry**

### **Volume 55, Issue 8**

#### **Combined Stimulant and Guanfacine Administration in Attention-Deficit/Hyperactivity Disorder: A Controlled, Comparative Study**

McCracken, et al.

This was an 8-week double-blind, 3-arm comparative trial that studied the hypothesis that combined effects of d-methylphenidate extended-release with guanfacine would be clinically superior to either monotherapy and would have equal tolerability. A total of 207 Seven to fourteen year olds with a DSM-IV diagnosis of ADHD were randomized to either guanfacine (1-3 mg/day), d-methylphenidate extended-release, or a combination with fixed flexible dosing. Outcome measures were the ADHD Rating Scale IV (ADHD-RS-IV) and the Clinical Global Impression-Improvement (CGI-I) scale. Combination therapy showed evidence of clinical benefit over monotherapy. Combination treatment had significantly greater reduction in inattentive ADHD symptoms compared to monotherapies, and a greater positive response on CGI.

#### **Male Eating Disorder Symptom Patterns and Health Correlates from 13-26 Years of age.**

Calso, et al.

This study's aim was to identify patterns of eating disorder behaviors in males from adolescence through young adulthood. Symptomatic patterns that were identified included: body image disturbance, binge eating/purging, and use of muscle-building products. Males in the Binge Eating/Purging and Muscularity-Concerns classes had high prevalence of binge drinking and drug use. Concerns about leanness, muscularity and use of muscle-building projects should be noted when assessing males for eating disorders.

## **Stressful Life Events During Pregnancy and Offspring Depression: Evidence from a Prospective Cohort Study**

Kingsbury, et al.

This study aimed to examine the association between mother's exposure to prenatal stressful life events and offspring depression. The sample consisted of 10,569 members of a prospective population-based cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC). Mothers were asked to report on the occurrence and impact of 42 prenatal stressful life events. Offspring depressive symptoms were assessed using a computerized version of the Clinical Interview Schedule-Revised (CIS-4) at age 17 to 18, as well as 13 self-report statements from the Short Mood and Feelings Questionnaire at 6 time points from ages 10 to 11 to 18 to 19. There was an association between a 1-unit increase in maternal stressful life events scores during gestation and increased offspring depressive symptoms and major depression at age 17 to 18.