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

**Journals Covered:**

- \* American Journal of Psychiatry (AJP)
- \* AJP – Resident’s Journal (RJ)
- \* JAMA Psychiatry (JAMA-P)
- \* Lancet Psychiatry (LP)
- \* Journal of the American Academy of Child & Adolescent Psychiatry (JAACAP)
- \* Miscellaneous: Stroke

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**Highlights**

- Microglial activity is elevated in patients with schizophrenia and in individuals at ultra high risk of psychosis, and is related to at-risk symptom severity. (AJP)
- Schizophrenia patients with genotypes associated with increased Kv11.1-3.1 genotypic expression and slow metabolizer status appear to show marked improvement in symptoms when treated with risperidone. (AJP)
- Baseline striatal connectivity predicts response to antipsychotic treatment in schizophrenia. (AJP)
- Case report describes naltrexone’s therapeutic efficacy for severe self-injurious behavior in Down’s syndrome. (RJ)
- Trauma during puberty predisposes to a higher risk for anxiety disorders in adolescent girls whereas trauma during the grade school period confers higher risk for depressive disorders. (JAACAP)
- Impairments in social activity and functioning in school or work are recognizable up to 15 years before first hospitalization for schizophrenia. Small, non-progressive deficits in these components are also seen in unaffected siblings. (JAMA-P)
- Suicide attempts and recurrent suicide attempts are associated with epilepsy even before epilepsy manifests. (JAMA-P)
- There appears to be a strong association of child neglect with cognitive deficits in childhood and adulthood. (JAACAP)
- Addition of lamotrigine to quetiapine improves symptoms in bipolar depression. Administration of folic acid, however, appears to diminish the additive effects of lamotrigine on quetiapine. (LP)
- Inspired by Hilbert’s problems in mathematics, Stephan and colleagues offer a list of priority problems in psychiatry. (LP)

- PTSD symptoms increase within first 6 months after deployment & then at 5 years after deployment. (LP)
- In a longitudinal study antidepressant use was associated with a higher incidence of cerebral microbleeds. (Stroke)

## **The American Journal of Psychiatry**

### **Volume 173, Issue 1**

#### **Prescription Opioid Misuse, Abuse and Treatment in the United States: An Update**

Brady, et al.

This review on the opioid epidemic in the United States provides initial reports that suggest the rates of opioid abuse and misuse have plateaued recently after escalating rates for the past 20 years. This is likely a result of public policy and education initiatives as well as changes in FDA treatment guidelines recommending long acting opioids be reserved for the treatment of severe pain and pharmacological treatment be combined with psychosocial interventions. Despite the initial signs of progress, there is still limited access and low utilization rates of treatment and research on treatment specifically for prescription opioid use disorders and their comorbidities such as chronic pain and depression is still limited.

#### **Association between ADHD and Obesity: A Systematic Review and Meta-Analysis**

Cortese, et al.

This meta-analysis reviewed 42 studies to determine the association between ADHD and obesity due to the possible increased food intake as a result of impulsivity and inattention in those with the disorder. Previous studies found mixed results. However, this review found a significant association between obesity and ADHD in both children (odds ratio-1.20, 95% CI=1.05-1.37) and adults (odds ratio-1.55, 95% CI=1.32-1.81.) Significant association was also found between ADHD and being overweight. However, individuals who were medically treated for ADHD were not found to be at higher risk.

#### **Microglial Activity in People at Ultra High Risk of Psychosis in Schizophrenia: An [<sup>11</sup>C]PBR28 PET Brain Imaging Study**

Bloomfield, et al.

This cohort PET imaging study found elevation of microglial activity in patients with schizophrenia as well as those presenting with subclinical symptoms who are at ultra high risk for psychosis compared to controls. The study also found that the degree of microglial activity is related to the at-risk symptom severity and suggests a link between neuroinflammation and the risk of psychosis.

#### **Differential Response to Risperidone in Schizophrenia Patients by KCNH2 Genotype and Drug Metabolizer Status**

Heide, et al.

This study tested the hypothesis that a slow metabolizer status along with gene variants of KCNH2 that led to increased expression of Kv11.1-3.1 potassium channels resulted in improved responses to antipsychotic medications. Of the 362 patients within the CATIE study, 52 were found to have increased

Kv11.1-3.1 expression and showed better treatment response. Approximately 7% of patients were found to have both increased Kv11.1-3.1 potassium channel expression and slow metabolizer status and showed marked symptom improvement when treated with risperidone compared to those who were fast metabolizers or did not have the KCNH2 risk genotype.

### **Baseline Striatal Functional Connectivity as a Predictor of Response to Antipsychotic Drug Treatment**

Sarpal, et al.

This cohort fMRI study evaluated 41 first-episode schizophrenia patients and 40 chronic schizophrenia patients with an acute episode of psychosis and developed whole-brain functional connectivity maps. Clinical response was monitored while the subjects received antipsychotic treatment. Results found that baseline striatal connectivity predicted response to antipsychotic treatment with high sensitivity and specificity in both cohorts and could potentially become a prognostic biomarker for treatment response.

### **Amygdala Activity during Autobiographical Memory Recall in Depressed and Vulnerable Individuals: Association with Symptom Severity and Autobiographical Overgenerality.**

Young, et al.

This fMRI study compared amygdala reactivity and connectivity during autobiographical memory recall in healthy control subjects, unmedicated currently depressed patients, unmedicated remitted depressed patients and individuals with high familial risk for developing depression. Results indicate that left amygdala hyperactivity during negative autobiographical recall is a trait-like marker of depression while amygdala hypoactivity during positive autobiographical recall is a state marker of depression manifesting in active disease.

## **The American Journal of Psychiatry - Resident's Journal**

### **Volume 11, Issue 1**

#### **Pharmacological Advances in the Treatment of Schizophrenia**

Ballester, et al.

Numerous drugs currently in development for schizophrenia have targets outside the dopaminergic system, and many are targeting negative and cognitive symptoms. Some of these medications include:

#### DOPAMINE SYSTEM

Phosphodiesterase (PDE) 10A Inhibitors

Eltoprazine (5-HT1A/1B Agonist) for cognitive impairment

Stepholidine (D2 antagonist, D1 agonist, 5HT1A agonist) for positive symptoms & cognition

## GLUTAMATE SYSTEM

Bitopertin: selective inhibitor of the glycine transporter Gly-T-1 that acts by increasing the levels of glycine in the synaptic cleft and potentiating NMDA receptor.

D-Amino Acid Oxidase Inhibitors (DAAOI) for treatment resistant schizophrenia

Positive Allosteric Modulator of Metabotropic Glutamate Receptors (mGluR2s) for residual negative symptoms

## ACETYLCHOLINE SYSTEM

Alpha-7 nAChR Agonists for cognitive deficits

Xanomeline (M1/M4 muscarinic receptor agonist) for cognition as well as psychotic symptoms

## SEROTONIN SYSTEM

5HT3 antagonists (ondansetron, granisetron, tropisetron): modulate neurotransmitter release, may be beneficial as augmentation agent

## HORMONES

LY500307 (selective estrogen beta agonist) for negative symptoms and cognition

Oxytocin: for improvement in social cognition and neurocognition

### **Naltrexone for Severe Eye-Gouging in Down Syndrome**

Hauptman A

Author presents the case of a profoundly intellectually disabled, nonverbal female patient with Down syndrome in her 40s who experienced life-long severe self-injurious behavior (SIB), including chronic eye-gouging that resulted in blindness. She had been unsuccessfully treated for decades with multiple medications (including neuroleptics, antidepressants, and anxiolytics). Subsequently she showed complete resolution of SIB with naltrexone therapy (50 mg/day), indicating its potential therapeutic role in this regard.

## **JAMA Psychiatry**

### **Volume 73, Issue 1**

#### **Structural Brain Connectivity as a Genetic Marker for Schizophrenia**

Bohlken, et al.

Study's goal was to determine if white matter integrity is associated with the genetic liability for development of schizophrenia. 70 sets of twins (discordant for schizophrenia) were compared to 130 individuals (data collected over 5 years). Connectivity and efficiency were assessed using diffusion-weighted imaging and measuring fractional anisotropy (a reflection of fiber density, axonal diameter and myelination of white matter). Results showed that low fractional anisotropy (decreased fiber density and myelination aka decreased connectivity) correlated with increased schizophrenia liability with 83.4%

correlation explained by common genes. Areas of the brain most commonly associated were the frontal, striatal, and thalamic regions.

### **Early Childhood Depression and Alterations in the Trajectory of Gray Matter Maturation in Middle Childhood and Early Adolescence**

Luby, et al.

Study examined the effects of early childhood depression (preschool to school age period) on cortical gray matter development from late school age to early adolescence. Data was collected on 193 children (90 were diagnosed with depression) ages 3-6 years who were observed for up to 11 years longitudinally. Findings showed marked alterations in cortical gray matter volume loss and thinning associated with MDD diagnosis prior to first MRI scan, thereby showing an association between early childhood depression and the trajectory of cortical gray matter development in late school age and early adolescence.

### **Epidemiology of DSM-5 Drug Use Disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions**

Grant, et al.

In this 2012-2013 cross-sectional National Epidemiologic Survey on Alcohol and Related Conditions–III (>36,000 adults interviewed), prevalences of 12-month and lifetime drug use disorder (DUD) were 3.9% and 9.9%, respectively. Prevalence was greater among men, white and Native American individuals, younger and previously or never married adults, those with lower education and income, and those residing in the Western US. Significant associations were found with MDD, dysthymia, Bipolar I, PTSD, antisocial personality, borderline personality, and schizotypal personality.

### **Developmental Trajectories of Impaired Community Functioning in Schizophrenia**

Velhorstk, et al.

This population-based, prospective study (which included a sibling-control comparison) examined 3 key components of community functioning: social activity, independent behavior, and functioning in school or work, in the years preceding first hospitalization for schizophrenia. Data from the Israeli National Draft Board Registry was linked with data from the Israeli Psychiatric Hospitalization Case Registry Among those with schizophrenia, impairments in social activity and functioning in school or work were recognizable up to 15 years before hospitalization. Independent behavior seemed preserved until the few years before first admission. Unaffected siblings had small impairments compared with controls in social activity and functioning in school or work scales; these were however non-progressive and unrelated to their affected sibling's time of illness onset.

### **Efficacy of Bright Light Treatment, Fluoxetine, and the Combination in Patients with Nonseasonal Major Depressive Disorder - A Randomized Control Trial**

Lam, et al.

This 8 week trial looked at adults aged 19-60 with nonseasonal MDD of at least moderate severity to determine the efficacy of light treatment (10,000 lux fluorescent white light box for 30 min/day in the morning), fluoxetine and a combination of both as determined by the change in score on the Montgomery-Åsberg Depression Rating Scale (MADRS). The results showed that bright light treatment, both in monotherapy and in combination with fluoxetine, were efficacious in treatment of nonseasonal MDD with relatively few side effects.

### **Effect of Early Adult Patterns of Physical Activity and Television Viewing on Midlife Cognitive Function**

Hoang, et al.

Participants with high television viewing over a 25 year period (high television watching is defined as watching >3 hours per day for more than two-thirds of visits) were more likely to have poor cognitive performance (<1 SD below the race-specific mean) on the Digit Symbol Substitution Test (DSST) and Stroop test, but not the Rey Auditory Verbal Learning Test. Low physical activity during 25 years (defined as activity levels below the lower, sex-specific baseline quartile for more than two-thirds of the of the visits) was significantly associated with poor performance on the DSST.

### **Occurrence and Recurrence of Attempted Suicide Among People with Epilepsy**

Hesdorffer, et al.

This population-based retrospective cohort study compared 14,059 case patients (who later had an onset of epilepsy) and 56,184 control cases, finding a 2.9 fold increased risk for a first a suicide attempt during the time period before the case patients received a diagnosis of epilepsy. There was also a 1.8 fold increased risk for recurrent suicide attempt up to and including the day that epilepsy was diagnosed. These results were in the absence of antiepileptic drugs and in the absence of diagnosed psychiatric disorders, suggesting a common underlying biology.

## **The Lancet Psychiatry**

### **Volume 3, Issue 1**

#### **Comparative evaluation of quetiapine plus lamotrigine combinations vs quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL); a 2 x 2 factorial randomized trial.**

Geddes, et al.

CEQUEL study (double-blind, randomized, placebo-controlled) aimed to determine if combination therapy with quetiapine plus lamotrigine leads to greater improvement in depressive symptoms over 12 weeks than quetiapine plus placebo in bipolar depression. Study shows that lamotrigine add-on therapy to quetiapine is effective at 3 months and that the improvement is sustained for at least a year. The study also investigated the additional effect of folic acid, and discovered that folic acid reduces the effectiveness of lamotrigine at 12 weeks.

**Post-traumatic Stress symptoms 5 years after military deployment to Afghanistan: an observational cohort study.**

Eekhout, et al.

In this observational cohort study Dutch military personnel who were deployed to Afghanistan were assessed for post-traumatic stress symptoms with the Self-Rating Inventory for Post-Traumatic Stress Disorder (SRIP) questionnaire. Participants were assessed 1 month before deployment and followed up at 1 month, 6 months, 12 months, 2 years and 5 years after deployment. Study revealed two symptom-peaks. A short-term symptom increase within the first 6 months after deployment, and a long-term symptom increase at 5 years after deployment. This underlines the importance of long-term monitoring of the psychological health of soldiers after deployment.

**Charting the landscape of priority problems in psychiatry, part 1: classification and diagnosis**

**Charting the landscape of priority problems in psychiatry, part 2: pathogenesis and aetiology**

Stephan, et al.

Inspired by successful examples of elucidating priority problems in other fields, such as the list of Hilbert's problems in mathematics, Klaas Stephan and colleagues offer a list of priority problems in psychiatry in two companion papers. These problems are listed as follows:

Problem 1: Is mapping between mental states and brain states computable?

Problem 2: What should be the status and role of symptoms in psychiatry?

Problem 3: Integrating a dimensional perspective on general psychopathology with categorical definitions of disease entities

Problem 4: Show that the brain manifests disease in limited ways (possibly only three or four)

Problem 5: Bridging the comparative gap: can preclinical models help to establish diagnostic criteria based on observable signs?

Problem 6: What is the higher order structure of fundamental mechanisms relevant for diagnostics?

Problem 7: New approaches to patient stratification are needed for neuroscience research

Problem 8: Develop computational assays for symptom-guided reassembly of psychiatric nosology

Problem 9: Computational assessment of learning dysfunctions for a dimensional perspective on psychiatric disorders

Problem 10: Derive a tractable account of the systems-level effect on the human brain of epidemiologically validated high-risk causal factors

Problem 11: What are the mechanisms of gene–environment interplay in psychiatry?

Problem 12: Understanding mechanisms of resilience

Problem 13: Can a mechanistic marker be found for diagnosis of schizophrenia and bipolar illness? What are the pitfalls?

Problem 14: What are the principles of cognitive-type microcircuits in a large-scale brain system, and how do their impairments explain mental disorders?

Problem 15: A Fokker-Planck equation for the brain

Problem 16: The problems of priors

Problem 17: Understanding psychiatric pathophysiology in terms of the computational processes that underlie inference

**Journal of the American Academy of Child and Adolescent Psychiatry**  
**Volume 55, Issue 1**

**Developmental Timing of Trauma Exposure Relative to Puberty and the Nature of Psychopathology Among Adolescent Girls**

Marshall, et al.

This study's objective was to determine whether exposure to potentially traumatic events during puberty predicts adolescent girls' psychopathology. The study examined a subset of 2,899 adolescent girls that participated in the National Comorbidity Survey Replication-Adolescent Supplement who completed the study two or more years postmenarche. Results indicated that compared to other developmental periods, trauma during puberty (defined 3 years before and year of menarche) predisposed to a significantly higher risk for adolescent girls' past year anxiety disorder diagnoses, whereas trauma during the grade school period (defined as 2-6 years before the puberty period) conferred significantly more risk for past-year depressive disorder diagnoses. Recency of trauma was the best predictor for past-year PTSD diagnoses.

**Child Neglect and Maltreatment and Childhood-to-Adulthood Cognition and Mental Health in a Prospective Birth Cohort**

Geoffroy, et al.

The objective of this prospective birth cohort study was to establish whether different forms of child maltreatment are associated with poorer cognition and educational qualifications in childhood/adolescence as well as whether these associations persisted in midlife. Using standardized tests, cognitive abilities at ages 7, 11, 16, and 50 years were assessed. The study found a strong association of child neglect with cognitive deficits from childhood to adulthood, even after adjusting for confounding factors and mental health. Childhood neglect and all forms of abuse were associated with poorer child-to-adulthood mental health, but abuse was mostly unrelated to cognitive abilities.

**School Achievement and Risk of Eating Disorders in a Swedish National Cohort**

Sundquist, et al.

In this Swedish national cohort study, high achievement in school was associated with increased risk of AN or BN. However, during the co-relative analysis as the degree of shared genetic and environmental factors increased, the association between school achievement and AN or BN substantially decreased, indicating that the association appears to be explained by unmeasured familial (genetic and environmental) factors.

## Miscellaneous

### **Antidepressant Use Is Associated With an Increased Risk of Developing Microbleeds**

Akoudad, et al.

Stroke. 2016;47(1):251-254

2559 participants aged  $\geq 45$  years, all without microbleeds at baseline, underwent baseline and repeat brain magnetic resonance imaging between 2005 and 2013 (mean time interval 3.9 years). Antidepressant use was associated with a higher cerebral microbleed incidence (odds ratio, 2.22; 95% confidence interval, 1.31–3.76) than nonuse.

*Research Watch* offers a unique publishing opportunity.

***Research Watch* is accepting submissions of commentary pieces in which authors can critically analyze and discuss recently published studies (within the last 6 months) related to psychiatry.**

#### **Guidelines:**

- Manuscripts can be authored by medical students, psychiatry residents, psychiatry fellows, or pharmacy students. The invitation is open to all medical schools, residency programs, fellowship programs in USA. Manuscripts authored by faculty members will not be considered. Guidance from faculty members can be acknowledged at the end of the manuscript.
- Up to 2 authors per manuscript are allowed.
- The manuscripts are limited to 500 words (main text, excluding references).
- Up to 5 references are allowed. References should be in Vancouver style.
- No abstract is required.
- Title Page should contain: Title, Author information and affiliation, word count, declaration of conflict of interest.
- One figure or one table is permitted.
- Generic rather than trade names of drugs should be used.
- Manuscripts should be submitted via email to Chief Curator Awais Aftab at muhammad.aftab@uhhospitals.org. Manuscript should be in word document or pdf format.

#### **Review Process:**

Submissions will be reviewed and edited by the Chief Curator Awais Aftab. Any questions, clarifications or decisions will be communicated to the corresponding author. Dr Keming Gao (Associate Professor, Psychiatry, CWRU School of Medicine) will serve as faculty advisor.

Please contact Chief Curator Awais Aftab with any queries.