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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)
- * AJP – Resident’s Journal (RJ)
- * JAMA Psychiatry (JAMA-P)
- * Lancet Psychiatry (LP)
- * Journal of the American Academy of Child & Adolescent Psychiatry (JAACAP)
- * Updates from APA and FDA

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Highlights

- Citalopram was found effective for reducing neuropsychiatric symptoms in a subset of patients with Alzheimer’s dementia. (AJP)
- Ultra-low-dose buprenorphine may effectively reduce suicidality in the short-term for suicidal patients. (AJP)
- Buprenorphine/samidorphan demonstrated efficacy in the treatment of refractory depression. (AJP)
- Maternal phosphatidylcholine supplementation during pregnancy may reduce attention deficit and social withdrawal behaviors in children. (AJP)
- Deep brain stimulation of the ventral anterior limb of the internal capsule was shown to improve treatment-resistant depression in a randomized clinical trial. (JAMA-P)
- N-acetylcysteine treatment resulted in significant reductions in skin-picking symptoms in excoriation disorder. (JAMA-P)
- Older adults with a longitudinal pattern of high and increasing depressive symptoms are at high risk for dementia. (JAMA-P)
- A taxonomy of putative biotypes of neural circuit dysfunction for depression and anxiety has been proposed. (LP)
- Gestational exposure to SSRIs may be linked to increased incidence of depression in the offspring. (JAACAP)
- Nuplazid (pimavanserin), a 5-HT_{2A} inverse agonist, has been approved by FDA for the treatment of hallucinations and delusions associated with Parkinson’s disease psychosis.
- APA has published *Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia*.
- FDA has issued warnings that olanzapine has been linked to a rare skin condition 'drug reaction with eosinophilia and systemic symptoms (DRESS)', and aripiprazole is associated with rare impulse control side effects.

The American Journal of Psychiatry

Volume 173, Issue 5

Heterogeneity of Treatment Response to Citalopram for Patients With Alzheimer's Disease with Aggression or Agitation: The CitAD Randomized Clinical Trial

Schneider, et al.

This double-blind parallel-group multicenter trial randomized 186 patients with Alzheimer's Disease and clinically significant agitation to receive either placebo or citalopram for 9 weeks with citalopram titrated to 30mg/day over the initial 3 weeks. The results found patients within the age range of 76-82 years in the outpatient setting with the least cognitive impairment and moderate agitation levels benefited from citalopram. Placebo was safer and more effective for study participants who were in long-term care facilities with more severe cognitive impairment and agitation and treated with lorazepam.

Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia: Evidence from the CitAD Study

Leonpacher, et al.

This secondary analysis of the CitAD study utilized caregiver-reported Neuropsychiatric Inventory scores to evaluate citalopram's effects on neuropsychiatric symptoms in Alzheimer's Dementia. The analysis revealed that at week 9, citalopram showed efficacy in reducing the frequency of irritability, anxiety, delusions and hallucinations but increased the severity of sleep/nighttime behavior disorders.

Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation: A Randomized Controlled Trial

Yovell, et al.

This randomized double-blind placebo-controlled trial administered ultra-low dose buprenorphine (initial dosage of 0.1mg daily or BID, with mean final dosage of 0.44mg/day) to severely suicidal patients without substance use disorders as an adjunctive treatment to subjects' ongoing individual treatment. Suicidal ideation was then assessed at 2 and 4 weeks and found those who received ultra-low dose buprenorphine had a greater reduction in Beck Suicide Ideation Scale scores. Concurrent use of antidepressants and a diagnosis of Borderline Personality Disorder did not affect the response and no withdrawal symptoms were reported after treatment discontinuation at the end of the trial.

Opioid Modulation With Buprenorphine/Samidorphan as Adjunctive Treatment for Inadequate Response to Antidepressants: A Randomized Double-Blind Placebo-Controlled Trial

Fava, et al.

This multicenter, randomized, double-blind, placebo-controlled, two-stage sequential parallel comparison study randomly assigned adult patients with major depression who were treatment refractory to one or

two courses of antidepressants to buprenorphine/samidorphan 2mg/2mg, 8mg/8mg or placebo and compared depressive symptoms to baseline after 4 weeks using the HAM-D, MADRS and CGI-S rating scales. Results showed there were significantly greater improvement in all 3 depression outcome measures in the group receiving the 2mg/2mg dosage compared to placebo but not the 8mg/8mg dosage. Buprenorphine/samidorphan was well tolerated and there was no evidence of opioid withdrawal following treatment discontinuation.

Perinatal Phosphatidylcholine Supplementation and Early Childhood Behavior Problems: Evidence for CHRNA7 Moderation

Ross, et al.

This double-blind, placebo-controlled trial randomized pregnant women at the end of their first trimester and with no self-reported illicit drug use in the prior 6 months, no alcohol dependence or current nicotine use to receive 3600mg phosphatidylcholine in the morning and 2700mg in the evening. Newborns assigned to the in utero phosphatidylcholine treatment group continued to receive 600mg of phosphatidylcholine until 3 months of age. When infants were at 40 months of age, parents within the phosphatidylcholine treatment group indicated fewer attention problems and less social withdrawal on the Child Behavior Checklist compared to their placebo counterparts. This suggests maternal phosphatidylcholine treatment may, by increasing activation of the alpha7-nicotinic acetylcholine receptor, alter the development of behavior problems in early childhood that could indicate later mental illness.

The American Journal of Psychiatry - Resident's Journal **Volume 11, Issue 5**

Patient-Targeted Googling and Psychiatry: A Brief Review and Recommendations in Practice

Cole A

This article discusses a framework who when and if patient-targeted googling is to assist in psychiatric clinical decision making. The author states that associated risks and ethical concerns of patient-targeted googling including the violation of patient privacy and harm to the psychotherapeutic relationship. The author suggests that casual searches for patient information should be avoided and reserved only when careful consideration is given to the risks and benefits before using googling. The author believes that any information received from googling the patient's name should be documented in the patient's medical record as well as informing the patient of what has been discovered from googling.

The Psychiatric Ramifications of Moral Injury Among Veterans

Delima-Tokarz T

The author of this article states it is important to differentiate moral injury from PTSD. Moral injury is the conflict caused by transgressions of one's moral code by an individual or leadership causing shame in the

patient, and can be broken up into organizational, environmental, cultural and relational, and psychological aspects. Screening tools are still being developed to gauge moral injury. By understanding the significance of the moral injury, the author believes that providers will gain insight into the psychopathology in veterans.

JAMA Psychiatry

Volume 73, Issue 5

Hydromorphone Compared With Diacetylmorphine for Long-term Opioid Dependence - A Randomized Clinical Trial

Oviedo-Joekes, et al.

This phase 3, double blind, noninferiority study conducted in Canada tested if injectable hydromorphone hydrochloride is noninferior to injectable diacetylmorphine (the active ingredient in heroin) in reducing illicit heroin use for chronic injection opioid users. The results suggested a noninferiority of injectable hydromorphone relative to diacetylmorphine for long-term opioid dependence. In locations where diacetylmorphine is currently not available (usually because of political and regulatory barriers) hydromorphone could be offered as an alternative.

Deep Brain Stimulation of the Ventral Anterior Limb of the Internal Capsule for Treatment-Resistant Depression A Randomized Clinical Trial

Bergfeld, et al.

Twenty five patients with treatment resistant depression were given DBS (either active treatment or sham) and depression response was measured using the HAM-D-17 depression rating. Mean HAM-D decreased from 22.2 at baseline to 15.9 ($p=.001$) during the optimization phase (bilateral implants of 4 contact electrodes followed by optimization of DBS until a stable response was achieved). Following the optimization phase, 10 patients (40%) were classified as responders. Then a 12-week crossover phase was conducted with 16 patients receiving active treatment followed by sham or vice versa. In the crossover phase, patients scored significantly lower on the HAM-D-17 scale during active DBS (13.6) than during sham DBS (23.1).

Observed Cognitive Performance and Deviation From Familial Cognitive Aptitude at Age 16 Years and Ages 18 to 20 Years and Risk for Schizophrenia and Bipolar Illness in a Swedish National Sample

Kendler, et al.

This population-based prospective cohort design found that the developmental processes that impact schizophrenia risk are not well indexed by cognitive performance measured in adolescence but are better reflected by the deviation in performance from that expected given the cognitive abilities of families. Familial cognitive aptitude is calculated from school achievement, IQ, and educational attainment in biological relatives.

N-Acetylcysteine in the Treatment of Excoriation Disorder: A Randomized Clinical Trial

Grant, et al.

A randomized, double blind trial was conducted to determine if N-acetylcysteine would be more effective than placebo in reducing compulsive picking behaviors. This amino acid is thought to restore extracellular glutamate in the nucleus accumbens. This trial included 66 adults with Skin Picking Disorder at ambulatory care centers who were treated with N-acetylcysteine, in doses ranging from 1200-3000mg/d, or placebo for 12 weeks. Participants were assessed using measures of skin-picking severity including the modified Yale-Brown Obsessive Compulsive Scale (NE-YBOCS) and the Clinical Global Impression-Severity Scale. Compared to placebo, treatment with N-acetylcysteine was associated with significant improvements in the NE-YBOCS, $p=0.048$. Compared to placebo, 47% of participant receiving the treatment were much or very much improved, $p=0.03$.

Trajectories of Depressive Symptoms in Older Adults and Risk of Dementia

Kaup, et al.

This prospective cohort study investigated the association between trajectories of depressive symptoms and the risk of dementia in older adults. Trajectories of depressive symptoms were assessed from baseline (mean age 74) to year 5 using the Center of Epidemiological Studies Depression Scale Short Form in a population of community-dwelling older adults. Results showed having a high and increasing depressive symptom trajectory was associated with a significantly increased risk of dementia (HR 1.94). Sensitivity analyses indicated that although the high and increasing trajectory was associated with dementia incidence, depressive symptoms at individual time points were not.

The Lancet Psychiatry

Volume 3, Issue 5

Brain-imaging studies of treatment-resistant schizophrenia: a systematic review

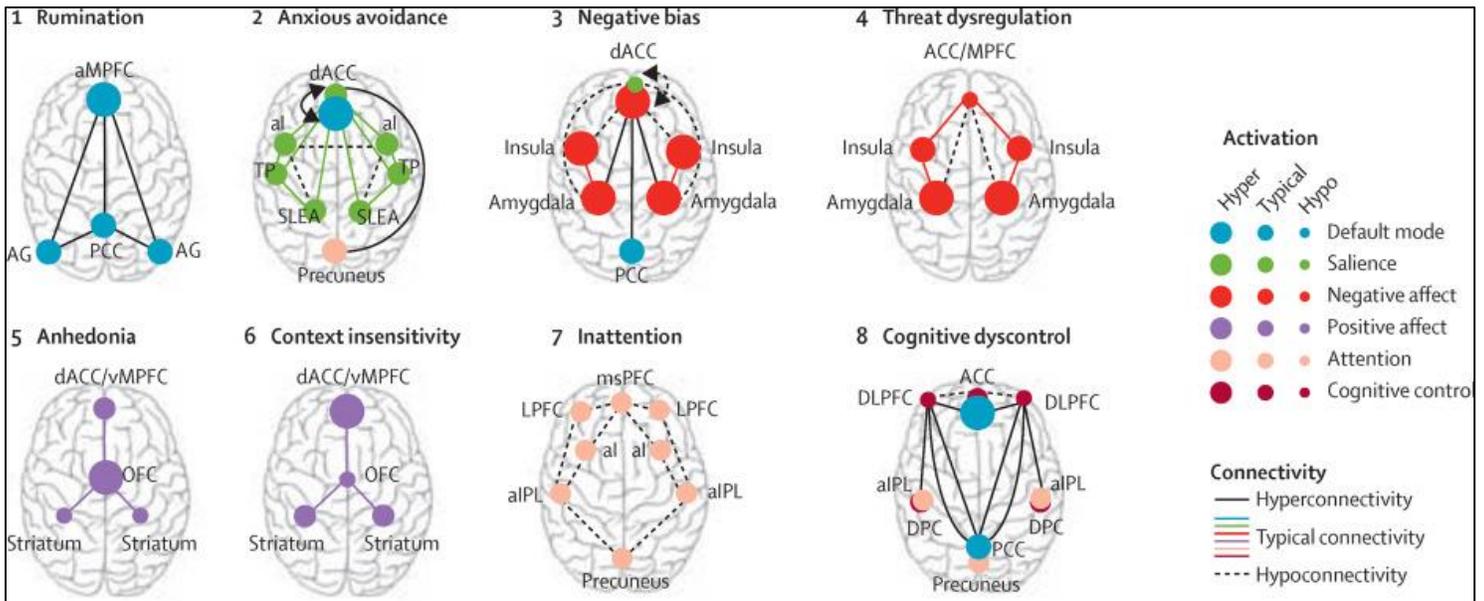
Mouchlianitis, et al.

This systematic review of brain-imaging studies of treatment-resistant schizophrenia report a number of neuroimaging features. Compared with treatment-responsive patients, treatment-resistant patients have: Grey matter reduction, particularly in frontal regions; increased white matter volume; reduced striatal dopamine synthesis; elevated glutamate concentration in the anterior cingulate cortex; glutamate and glutamine concentrations are increased in the putamen and decreased in the dorsolateral prefrontal cortex in clozapine responders. There is also reduced prefrontal atrophy in clozapine responders compared with non-responders. Some of the neurobiological changes seen in treatment-resistant schizophrenia are on a continuum with treatment-responsive schizophrenia, whereas some differences are categorical in nature and have potential to be used as biomarkers.

Precision psychiatry: a neural circuit taxonomy for depression and anxiety

Williams LM.

Author proposes a taxonomy of putative biotypes of neural circuit dysfunction for depression and anxiety. This taxonomy specifies symptoms in terms of underlying neural dysfunction at the individual level, and reflects the heterogeneity of depression and anxiety. The taxonomy is summarized in the figure below.



Effect of antidepressant treatment on cognitive impairments associated with depression: a randomised longitudinal study

Shilyansky, et al.

In this randomized longitudinal study, which was part of the iSPOT-D trial, investigators assessed cognitive function before and after 8 weeks of treatment with either escitalopram, sertraline, or venlafaxine extended-release. None of the 3 antidepressants demonstrated an improvement in cognitive function.

Trajectories of suicidal ideation in patients with first-episode psychosis: secondary analysis of data from the OPUS trial

Madsen, et al.

Using longitudinal data from the prospective 10-year follow-up OPUS trial of young Danish patients with first-episode psychosis, authors identified three trajectories for suicidal ideation. Low-decreasing trajectory (61%), frequent-stable trajectory (33%) and frequent-increasing trajectory (6%). The risk of persistent suicidal ideation and suicide attempt was higher for patients in the frequent-stable and frequent-increasing classes at 5 years.

Journal of the American Academy of Child and Adolescent Psychiatry

Volume 55, Issue 5

Impact of a Mental Health Curriculum on Knowledge and Stigma Among High School Students: A Randomized Controlled Trial

Milin, et al.

The objective of this study was to evaluate the effectiveness of a school-based mental health literacy intervention for adolescents on knowledge and stigma. There were a total 24 high schools and 534 students in Ottawa, Canada who participated in this trial. Schools were randomly assigned to either the curriculum or control condition. Outcomes measured included change in mental health knowledge and stigma which were assessed via a posttest questionnaire. Results indicated a significant change in stigma scores over time with positive attitudes toward mental illness increasing as a result of the curriculum. There was also a significant change in knowledge scores over time. Results support the implementation of such a curriculum in high schools.

Gestational Exposure to Selective Serotonin Reuptake Inhibitors and Offspring Psychiatric Disorders: A National Register-Based Study

Malm, et al.

This cohort study used a national register data in Finland between 1996-2010 to investigate the impact of gestational exposure to SSRIs on offspring neurodevelopment. There were categories of pregnant women and their offspring: SSRI exposed + exposed to psychiatric disorder, no antidepressant exposure, exposed to SSRIs only before pregnancy, and unexposed to antidepressants and psychiatric disorders. The cumulative incidence of depression among offspring exposed prenatally to SSRIs was 8.2% by age 14.9 years, compared with 1.9% in the psychiatric disorder with no medication group. Findings did not suggest that prenatal SSRI exposure was associated with increased rates of anxiety, autism spectrum disorder, and ADHD. However, authors note that these findings must be balanced against the risks of untreated maternal depression.

News and Updates

- NUPLAZID (pimavanserin) has been approved by FDA for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. The effect of pimavanserin is believed to be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors.
- APA has published *Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia*. Aside from reinforcing principles of good clinical practice, some recommendations stand out: Clinicians are recommended to use a quantitative measure to track symptoms and response to treatment. There is recommendation to attempt tapering and

stopping an antipsychotic medication within 4 months of initiation. In the absence of delirium and for non-emergency use, haloperidol is not to be used as a first line agent. These guidelines are available online on APA's website:

<http://psychiatryonline.org/doi/book/10.1176/appi.books.9780890426807>

- FDA has issued a warning that olanzapine has been linked to a rare skin condition 'drug reaction with eosinophilia and systemic symptoms (DRESS)' with 23 cases of DRESS reported with olanzapine worldwide since 1996.
- FDA has issued a warning that aripiprazole is associated with rare impulse control side effects such as compulsive gambling, eating, shopping, and sexual activity.
- Vortioxetine's brand name has been changed from Brintellix to Trintellix to avoid confusion with the antiplatelet drug Brilinta.