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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)
- * 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
- * Nature
- * Updates from FDA

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Highlights

- Systematic review supports the adjunctive use of S-adenosylmethionine (SAME), methylfolate, omega-3, and vitamin D in the treatment of depression. (AJP)
- Antipsychotic and antidepressant use is associated with lower overall mortality, whereas chronic high-dose use of benzodiazepines is associated with higher mortality in patients with schizophrenia. (AJP)
- Women with severe postpartum psychiatric disorders have increased mortality rate ratios, with particularly high relative risk for suicide in the first year. (AJP)
- In a large UK population-based longitudinal study using electronic health records, maintenance treatment in bipolar disorder with lithium is shown to have reduced rates of self-harm and unintentional injury compared to valproate, olanzapine, and quetiapine. (JAMA-P)
- Altered connectivity in visual-limbic subnetwork during emotional face processing is proposed as an intermediate phenotype for schizophrenia, and social perception circuit activity is suggested as a neurobiological marker for autism spectrum. (JAMA-P)
- Clozapine, thioridazine and haloperidol show a higher risk of antipsychotic-related seizures compared to risperidone & other atypicals. (JCP)
- Investigators develop a predictive model of violent reoffending on release from prison, available online for free as OxRec. (LP)
- One-year follow-up of TOSCA trial showed no differences in parent-reported behavioral outcomes between stimulant + placebo and stimulant + risperidone in the treatment of ADHD with severe physical aggression. (JAACAP)
- FDA has approved Probuaphine, a six-month buprenorphine implant, for the maintenance treatment of opioid dependence, for patients who are already stable on buprenorphine.
- Ketamine metabolite hydroxynorketamine is shown to exert antidepressant activity in mice independent of NMDA antagonism. (Nature)

The American Journal of Psychiatry

Volume 173, Issue 6

Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses

Sarris, et al.

This systematic review and meta-analysis concluded there is positive evidence that concurrent use of S-adenosylmethionine, methylfolate, omega-3 or vitamin D with antidepressants reduces depressive symptoms. Mixed results were found for zinc, folic acid, vitamin C and tryptophan.

Mortality and Cumulative Exposure to Antipsychotics, Antidepressants, and Benzodiazepines in Patients with Schizophrenia: An Observational Follow-Up Study

Tiihonen, et al.

This study calculated all-cause and cause-specific mortality rates as a function of cumulative low, moderate and high exposure to antipsychotics, antidepressants and benzodiazepines in 21,492 patients with Schizophrenia in Sweden from 2006 through 2010. Results show that moderate and high-dose antipsychotic and antidepressant use were associated with 15%-40% lower overall mortality, whereas chronic high-dose use of benzodiazepines was associated with up to 70% higher risk of death compared to no exposure. However, the authors note that the findings for benzodiazepines may be a result of residual confounding due to a higher intrinsic risk of death in patients with depression and anxiety.

Accelerated Brain Aging in Schizophrenia: A Longitudinal Pattern Recognition Study

Schnack, et al.

This longitudinal imaging study included subjects age 16 through 67 years with and without Schizophrenia and utilized machine learning algorithms to build models to predict brain age and the presence of Schizophrenia based off of gray matter density maps. Results showed that brain age was significantly greater than chronological age in Schizophrenia patients and progressively increased with follow up. The study also found that the acceleration of brain age was not constant as there was more accelerated brain aging in the first year of illness that then normalized approximately 5 years after illness onset.

Depressive and Anxiety Disorders Showing Robust, but Non-Dynamic, 6-Year Longitudinal Association with Short Leukocyte Telomere Length

Verhoeven, et al.

This longitudinal study included 2292 patients with remitted and current diagnoses of depressive or anxiety disorders and 644 healthy control subjects and assessed subjects' leukocyte telomere length (LTL) using quantitative PCR at baseline and at 6 years follow up. The results showed that subjects with remitted and current depressive or anxiety disorder had consistently shorter LTL and remained significant when

controlled for lifestyle and health variables. The shorter LTL is suggested to either be a long-term consequence or an underlying vulnerability factor for depressive or anxiety disorders.

Effect of Hippocampal and Amygdala Connectivity on the Relationship Between Preschool Poverty and School-Age Depression

Barch, et al.

Study tested the hypothesis that poverty experience during childhood has an impact on functional brain connectivity later during school age, which then mediates influences on child negative mood/depression. Participants were preschoolers, ages 3-5 years, obtained from primary and daycare centers in St. Louis who were then underwent annual behavioral assessments for 12 years. Using functional MRI during school age, findings showed that poverty (lower income-to-needs ratio) at preschool age was associated with reduced connectivity between the hippocampus and amygdala and several areas (superior frontal cortex, lingual gyrus, posterior cingulate, and putamen) during school age. Poverty predicted greater negative mood/depression severity at school age which was mediated by connectivity between the left hippocampus and right superior frontal cortex and between the right amygdala and right lingual gyrus.

All-Cause Mortality in Women With Severe Postpartum Psychiatric Disorders

Johannsen, et al.

Authors compared mortality rates of women with first-onset severe psychiatric disorders following childbirth with other female psychiatric illness. This Danish register-based cohort study identified women with first-time psychiatric illness in 0-3 months postpartum and measured mortality rate ratios (MMR): deaths from natural causes or unnatural causes, i.e. suicides, accidents, and homicides. Women with postpartum psychiatric disorders had a higher MMR (3.74) compared to non postpartum onset mothers (MMR=2.73) when compared to mothers with no psychiatric history. Interestingly, childless women with psychiatric diagnoses had the highest MMR at 6.15. Overall, results from women with postpartum psychiatric disorders showed that within the first year of diagnosis, suicide risk was increased (MMR=289) when compared with mothers with no psychiatric history. No homicides were reported for this group of 2699 women; 59.4% of the women with postpartum psychiatric disorders died from natural causes.

G-CSF Dosing to Prevent Recurrent Clozapine-Induced Agranulocytosis

Freeman et al.

This is a case report of a 19 year old man with Schizoaffective disorder who achieved long term stabilization of psychiatric symptoms using clozapine with granulocyte colony -stimulating factor (G-CSF). Nine months after Clozapine initiation, agranulocytosis occurred. Clozapine was re-initiated with twice-weekly injections 300 µg G-CSF (5.6 µg/kg/week), however, agranulocytosis occurred again. Eventually, an dose of 480 µg G-CSF twice weekly (9 µg/kg/week) was used with ANC parameters: goal ANC 5,000-30,000 cells/µL and hold G-CSF for ANC >25,000 cells/µL. Eventually ANC stabilized (with concurrent use of 700mg clozapine daily dose) using 480 µg G-CSF (6.4 µg/kg/week) every 5 days with weekly CBC monitoring.

The American Journal of Psychiatry - Resident's Journal

Volume 11, Issue 6

Heavy-Drinking Smokers: Pathophysiology and Pharmacologic Treatment Options

Mirbaba M

Heavy-drinking smokers are defined as women who drink >7 alcoholic beverages per week and >3 drinks on one occasion and men who drink >14 alcoholic beverages per week and >4 drinks on one occasion at least once weekly (in the past 30 days) and smoke at least 10 cigarettes daily. The combination of alcohol and tobacco use put this population at higher risk of health consequences than those who use alcohol or tobacco alone. Possible treatment options to address this population include varenicline plus oral naltrexone, or off label use of topiramate monotherapy (though needs further studies). Naltrexone works through Mu-opioid receptor antagonism with kappa-opioid receptor partial agonism and blocks rewarding effects of alcohol and nicotine in the nucleus accumbens. Varenicline is a partial agonist of multiple nAChRs, including $\alpha 4\beta 2$ and $\alpha 6\beta 2$ and is believed to reduce the ability of nicotine and alcohol to activate mesolimbic pathways. Topiramate acts by blocking AMPA/kainate glutamatergic receptors and facilitating GABA-A neurotransmission, the former of which may reduce the AMPA mediated ventral tegmental area activation by alcohol and nicotine co-use.

Adolescents “Dabbing” With Marijuana: A Novel Mechanism for Smoking Highly Concentrated Tetrahydrocannabinol

Furey K

Dabbing is a mode of marijuana ingestion in which individuals inhale a highly concentrated form of tetrahydrocannabinol (THC) from vaporized butane hash oil (colloquially called dabs, earwax, budder, shatter) created via butane extraction. Dabs contain THC concentrations up to 23%–80%, compared to the 3%–6% seen in traditionally smoked cannabis. Up to 40% of the THC can be inhaled, based on controlled experiments. Recreational users can synthesize dabs at home through a process known as blasting, with directions easily found via Internet search. There are many safety concerns surrounding dabbing, including the fire hazard of the blasting process, increased withdrawal and tolerance symptoms, addiction risks, and associations with psychosis.

Ayahuasca: Friend or Foe?

Fernando G

Ayahuasca is a chemical substance used in a religious, shamanic, or spiritual context that can induce hallucinations and spiritual experiences that are thought to be due to increased introspection, which has become more popular in South America. Ayahuasca is believed to cause increased somatic awareness and emotional arousal by activating bilateral anterior insula/inferior frontal gyrus, anterior cingulate/medial frontal gyrus in the right hemisphere, and amygdala/parahippocampal gyrus in the left hemisphere.

Ayahuasca contains MAOA-inhibiting beta-carbolines, but can also be combined with other leaves containing high concentrations of N-dimethyltryptamine. While popular culture has supported its expanding use, it can lead to significant medical complications, such as serotonin syndrome and death.

JAMA Psychiatry

Volume 73, Issue 6

Self-harm, Unintentional Injury, and Suicide in Bipolar Disorder During Maintenance Mood Stabilizer Treatment: A UK Population-Based Electronic Health Records Study

Hayes et al.

Study conducted to compare rates of self-harm, unintentional injury, and suicide in patient with bipolar disorder who were prescribed lithium, valproate sodium, olanzapine, or quetiapine fumarate when used for maintenance treatment. Results in a cohort of 6671 showed that self-harm rates were lower in patients prescribed lithium compared to those prescribed valproate, olanzapine, or quetiapine. Unintentional injury rates were lower for lithium when compared with valproate and quetiapine, but not olanzapine. There were too few suicide events to allow for accurate estimates of rates amongst maintenance medications. Bottom line: These findings support smaller observational study results and suggests that lithium can reduce impulsive aggression in addition to stabilizing mood.

Prediction of Individual Response to Electroconvulsive Therapy via Machine Learning on Structural Magnetic Resonance Imaging Data

Redlich, et al.

This nonrandomized prospective study investigated whether certain factors identified by structural magnetic resonance imaging (MRI) techniques were able to predict ECT response to depression based on HAM-D scores. It showed a positive association between pretreatment subgenual cingulate volume and individual ECT response ($p < .001$), indicating that a relatively small degree of structural impairment in the subgenual cingulate cortex before therapy seems to be associated with successful treatment with ECT.

Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse - An Individual Patient Data Meta-analysis From Randomized Trials

Kuyken, et al.

This meta-analysis examined the efficacy of mindfulness-based cognitive therapy (MBCT) versus usual care and other treatments, including antidepressants, in treatment of recurrent depression in 1258 patients. The results showed MBCT was efficacious as a treatment for relapse prevention for those with recurrent depression, particularly those with more pronounced residual symptoms.

Altered Functional Subnetwork During Emotional Face Processing - A Potential Intermediate Phenotype for Schizophrenia

Cao, et al.

This study examined 58 unaffected first-degree relatives of patients with schizophrenia and 94 healthy controls with an emotional face-matching f-MRI paradigm. It identified a cluster - mainly in the limbic system, the visual cortex and then subcortex - that showed significantly decreased coupling in relatives of patients with schizophrenia compared with controls ($p = .006$). This indicates that altered connectivity in a visual-limbic subnetwork during emotional face processing may be a functional connectomic intermediate phenotype for schizophrenia. These differences were not seen at a global level.

Evaluation of Quantified Social Perception Circuit Activity as a Neurobiological Marker of Autism Spectrum Disorder

Björnsdotter, et al.

It has been previously noted that there is a reduction in brain responses to biological motion in children with autism spectrum disorder (ASD), and this study theorized that this reduction may be robust enough to serve as an individual level marker of ASD. It was tested using MRI brain responses to point-light displays of coherent vs. scrambled human motion. A relative reduction in social perception circuit responses was identified in discovery cohort boys with ASD ($p = .01$), though typically developing girls and girls with ASD could not be distinguished ($P = .54$). In addition, brain responses were associated with social behavior in boys but not in girls.

The Journal of Clinical Psychiatry

Volume 3, Issue 5

Comparative Risk of Seizure With Use of First- and Second-Generation Antipsychotics in Patients With Schizophrenia and Mood Disorders

Wu, et al.

This study from Taiwan compared the risk of new seizure onset within 12 months of starting an antipsychotic using a population health claims database. The overall 1-year incidence rate of antipsychotic-related seizure (ARS) was 9.6 (95% CI, 8.8–10.4) per 1,000 person-years. Clozapine (aHR = 3.06), thioridazine (aHR = 2.90), and haloperidol (aHR = 2.34) had higher ARS risks than risperidone, whereas aripiprazole had a marginally lower ARS risk. [aHR= adjusted hazard ratio]

The Lancet Psychiatry

Volume 3, Issue 6

Prediction of violent reoffending on release from prison: derivation and external validation of a scalable tool

Fazel, et al.

By conducting a cohort study of a population of released prisoners in Sweden, investigators developed a predictive model for violent reoffending. At 2 years the model showed a sensitivity of 67% and specificity of 70%, with positive and negative predictive values being 37% and 89%, respectively. The model is available online for free as OxRec risk calculator: <http://oxrisk.com/oxrec/>

Journal of the American Academy of Child and Adolescent Psychiatry

Volume 55, Issue 6

Severely Aggressive Children Receiving Stimulant Medication Versus Stimulant and Risperidone: 12-Month Follow-Up of the TOSCA Trial

Gadow, et al.

This study evaluated clinical outcomes at 52-week follow-up of the TOSCA Study (Treatment of Severe Childhood Aggression), which began with a controlled, 9-week clinical trial comparing the relative efficacy of parent training + stimulant medication + placebo versus parent training + stimulant + risperidone as a treatment for children with co-occurring ADHD, disruptive behavior disorder, and serious physical aggression. Both randomized groups improved from baseline to follow-up. Although more participants in the risperidone augmentation group had lower CGI scores, the primary parent-reported behavioral outcomes showed no significant between-group differences.

Journal of the American Psychoanalytic Association

Volume 64, Issue 2

A Special Sort of Forgetting: Negation in Freud and Augustine

Rosengart D

Rosengart considers memory and forgetting as being two halves of the same whole by considering two thinkers. Highlighting the similarities between Freud's concept of repression and Augustine's of forgetting (as described in Confessions), Rosengart eventually places the two in tension – asserting that Freud's concept of the unconscious is fundamentally different from Augustine's interiority.

The Insane Look of the Bewildered Half-Broken Animal

Moss D

In his plenary address to the annual meetings of the American Psychoanalytic Association, Moss considers psychoanalysis' place in contemporary society. With particular attention to various desperate states of affairs worldwide, Moss seeks to legitimate the field's claim to relevance.

Miscellaneous

NMDAR inhibition-independent antidepressant actions of ketamine metabolites

Zanos, et al.

Nature. 533, 481–486 (26 May 2016)

Ketamine is an NMDAR antagonist with rapid antidepressant effects. Investigators in this paper share their discovery that the metabolism of ketamine to (2S,6S;2R,6R)-hydroxynorketamine (HNK) is essential for its antidepressant activity. (2R,6R)-HNK exerts rapid and sustained antidepressant actions in mice. These effects are NMDAR-independent but require AMPAR activation. Furthermore, (2R,6R)-HNK lacks the side effects associated with ketamine. This has the potential to offer new options for the development of novel rapid-acting antidepressants.

News and Updates

- FDA has approved Probuphine, the first buprenorphine implant for the maintenance treatment of opioid dependence. It is designed to provide a constant, low-level dose of buprenorphine for six months in patients who are already stable on low-to-moderate doses of other forms of buprenorphine. For more details:

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm503719.htm>