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Chief Curators:

Awais Aftab & Erin Fulchiero

Curators:

Christine Collins
Heather Wobbe
Javier Ponce Terashima
Prakash Mishra
Rob Siedler
Shanna Swaringen

Research Watch is an initiative by the residents of University Hospitals Cleveland 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)

Contact:

muhammad.aftab@uhhospitals.org
erin.fulchiero@uhhospitals.org

Highlights

- Meta-analysis of antipsychotic trials in acute schizophrenia over past 60 years shows stable response rates with only 23% of antipsychotic-treated subjects experiencing at least 50% improvement. (AJP)
- Study suggests PMDD symptoms are precipitated by acute changes in ovarian steroids rather than persistently elevated levels. (AJP)
- Study shows nearly twofold higher mortality rate among individuals with treatment-resistant schizophrenia not being treated with clozapine compared with clozapine-treated individuals. (AJP)
- Study indicates older adults who have a higher purpose in life show reduced risk of functional decline from an adequate baseline level of physical function. (JAMA-P)
- Population-based cohort study suggests that elevated risk of intellectual disability in children with prenatal antidepressant exposure is likely attributable to factors underlying the treatment. (JAMA-P)
- A Danish study suggest that low lithium concentrations in drinking water may be associated with an increased risk of dementia. (JAMA-P)
- Meta-analysis of 66 studies shows antidepressant response rates of 45-50% with acute sleep deprivation in depression. (JCP)
- Higher baseline proinflammatory cytokines are associated with poor antidepressant response to total sleep deprivation and light therapy in bipolar disorder. (JCP)
- Psychotic symptoms are associated with frontoparietal functional connectivity alterations in anti-NMDA receptor encephalitis. (LP)
- Meta-analysis ranks the risk of suicide attempts in juvenile mood disorder patients: BD > MDD > hypomania or mania-only > juvenile general population. (JAACAP)
- In an open-label extension trial of youth with ASD on atypical antipsychotics, subjects continued on metformin maintained their BMI, and those switched to metformin from placebo experienced improvement in BMI. (JAACAP)

The American Journal of Psychiatry
Volume 174, Issue 10

State-Independent and Dependent Neural Responses to Psychosocial Stress in Current and Remitted Depression

Ming, et al.

The objective of this study was to explore the state-independent (trait) and dependent (state) neural responses to psychosocial stress in major depressive disorder. 36 patients with medication-naive first-episode current depression, 33 patients with remitted depression, and 36 healthy controls were administered the Montreal Imaging Stress Task during functional MRI. Compared with control subjects, both current and remitted depression patients reacted more strongly to stress and exhibited similar brain activity patterns of hypoactivation of the ventromedial prefrontal cortex and hyperactivation of the precuneus suggesting that these regional brain activation changes may represent a state independent trait effect of depression that is independent of clinical status. In contrast, hyperactivation in the striatum and dorsolateral prefrontal cortex was only observed in remitted patients but not in depressed patients, suggesting that these regional brain activation changes may represent state-dependent neural responses to stress in depression.

Premenstrual Dysphoric Disorder Symptoms Following Ovarian Suppression: Triggered by Change in Ovarian Steroid Levels But Not Continuous Stable Levels

Schmidt, et al.

A seminal study of women with Premenstrual dysphoric disorder (PMDD) attempted to determine whether symptoms are triggered by an acute change in ovarian steroid levels or by levels, which stably exceed a critical threshold after gonadotropin-releasing hormone (GnRH) ovarian suppression. They hypothesize that excessive levels allow expression of an infradian affective “pacemaker”. Investigators prospectively studied 22 women, ages 30-50 years, with PMDD (DMS-IV). After 2-3 months of GnRH-agonist-induced ovarian suppression with 3.75mg of leuprolide, 12 women with symptom remission received 1 month of single-blind placebo, then 3 months of combined estradiol/progesterone. Self- and observer-rated scores on the Rating for Premenstrual Tension scale demonstrated increased symptoms during the first month of combined estradiol/progesterone therapy relative to the last month of leuprolide alone, placebo month, and the second and third months of estradiol/progesterone. Results indicate that the change in levels of estradiol and progesterone from low to high, rather than steady-state levels, that was critical in triggering PMDD symptoms.

Mortality and Self-Harm in Association with Clozapine in Treatment-Resistant Schizophrenia
Wimberly, et al.

Authors evaluated the rates of all-cause mortality and self-harm associated with clozapine treatment in individuals with treatment-resistant schizophrenia. Among a population-based cohort of 2,370

individuals with treatment-resistant schizophrenia, the rate of all-cause mortality was higher for those not receiving clozapine than those given clozaril (HR: 1.88, 95% CI: 1.16-3.05). Results were driven by periods without antipsychotic treatment (HR: 2.50, 95% CI: 1.50-4.17) with non-significantly higher mortality during treatment with other antipsychotics (HR: 1.45, 95% CI: 0.86-2.45). Excess mortality was noted in the year after clozapine discontinuation (HR: 2.65, 95% CI: 1.47-4.78), and self-harm was higher for non-clozapine antipsychotics than for clozapine (HR: 1.36, 95% CI: 1.04-1.78).

Sixty Years of Placebo-Controlled Antipsychotic Drug Trials in Acute Schizophrenia: Systematic Review, Bayesian Meta-Analysis, and Meta-Regression of Efficacy Predictors

Leucht, et al.

The authors present a meta-analysis of all placebo-controlled trials in patients with acute exacerbations of schizophrenia. Potential moderators of efficacy were analyzed by meta-regression. The analysis included 167 double-blind randomized controlled trials with 28,102 participants. The standardized mean difference (SMD) for efficacy was 0.38 after accounting for small-trial effects and publication bias. At least a “minimal” response (20% reduction in symptoms) occurred in 51% of the antipsychotic group versus 30% in the placebo group, and 23% versus 14% had a “good” response (50% reduction in symptoms). Positive symptoms (SMD 0.45) improved more than negative symptoms (SMD 0.35) and depression (SMD 0.27). In multivariable meta-regression, industry sponsorship and increasing placebo response were associated with reduced effect sizes. Drug response remained stable over time.

JAMA Psychiatry

Volume 74, Issue 10

Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents: A Systematic Review and Meta-analysis

Locher, et al.

This systematic review and meta-analysis identified 36 randomized, double-blind, placebo-controlled trials (n=6,778) to assess the relative efficacy and safety of SSRIs, SNRIs, and placebo for the treatment of Depressive Disorder (17 RCT's), Anxiety Disorder (10 RCT's), OCD (8 RCT's), and PTSD (1 RCT) in children and adolescents. Combined analysis yielded a statistically significant drug-placebo difference, such that SSRIs and SNRIs were more beneficial but with a small effect size ($g = 0.32$; 95% CI, 0.25-0.40; $p < .001$). The drug-placebo difference in effect size for Anxiety Disorder was significantly larger than for Depressive Disorder ($g = 0.20$; 95% CI, 0.13-0.27; $p < .001$). Patients with Depressive Disorder exhibited significantly larger placebo responses compared with those with Anxiety Disorder. Comparison of SSRIs and SNRIs showed no statistically significant difference in the Depressive Disorder group, but SSRIs were statistically superior to SNRIs in the Anxiety Disorder group. No studies investigated the use of SNRIs in OCD. Patients receiving an antidepressant reported significantly more treatment-emergent adverse events, severe adverse events (RR, 1.76; 95% CI, 1.34-2.32; $p < .001$), and study discontinuation due to

adverse events (RR, 1.79; 95% CI, 1.38-2.32; $p < .001$).

Effectiveness of Psychological and/or Educational Interventions in the Prevention of Anxiety: A Systematic Review, Meta-analysis, and Meta-regression

Moreno-Peral, et al

Authors present the first systematic review and meta-analysis examining the effectiveness of preventive psychological and/or educational interventions for anxiety across the lifespan. The review identified 29 randomized controlled trials including 10,430 patients from 11 countries on 4 continents. Most interventions were based on the principle of cognitive behavioral therapy (in 25 RCTs), whereas a few were based on other types of interventions (2 psychoeducational, 1 acceptance and commitment therapy, and 1 biopsychosocial). Outcomes were incidence of new cases of anxiety disorders or reduction of anxiety symptoms as measured by validated instruments. Overall, psychological and/or educational preventive interventions for anxiety showed a small, but statistically significant effect size compared to controls, with substantial heterogeneity in results between studies.

Association Between Purpose in Life and Objective Measures of Physical Function in Older Adults

Kim, et al.

Data from the Health and Retirement Study, a nationally representative longitudinal cohort study of US adults older than 50 years, were collected in 2006 and again in 2010. Data analysis was conducted to assess whether higher purpose in life among adequately functioning older adults is associated with lower risk of developing declines in physical function (weak grip strength and slow walking speed) during the 4-year follow-up period. Analyses were conducted using two samples of older adults who had scores at baseline indicating adequate function for each of two measurements, one for grip strength ($n=4,486$) and another for walking speed ($n=1,461$). Purpose in life was assessed at baseline using the Purpose in Life subscale of the Ryff Psychological Well-being Scales. After controlling for sociodemographic factors (age, sex, race/ethnicity, marital status, educational level, and total wealth), each 1-SD increase in Purpose in Life score was associated with a 13% decreased risk (95% CI, 1%-23%) of developing weak grip strength and a 14% decreased risk (95% CI, 8%-20%) of developing slow walking speed. Associations with walking speed were maintained in all covariate models (fully adjusted model: 11% decreased risk (95% CI, 5%-17%), but associations with grip strength did not reach statistical significance after adjusting for relevant baseline health factors, depressive symptoms, and health behaviors (fully adjusted model: risk ratio, 0.91; 95% CI, 0.80-1.04).

Effectiveness and Safety of Dementia Care Management in Primary Care: A Randomized Clinical Trial

Thyrian, et al.

In this study, 6,838 patients with principal diagnoses of dementia were randomized to a Dementia Care Management (DCM) group or a care as usual group. DCM is a collaborative care model, which uses a computer-assisted assessment to determine a personalized array of interventions and monitors the success of these interventions. Quality of life, caregiver burden, behavioral and psychological symptoms

of dementia, pharmacotherapy with anti-dementia drugs, and use of potentially-inappropriate medication were assessed. Results demonstrated that DCM significantly decreased behavioral and psychological symptoms of dementia, as well as caregiver burden. DCM patient also had an increased chance of receiving anti-dementia drug treatment. Those DCM patients not living alone had significantly increased quality of life. Overall, patients receiving DCM did not experience an increase in quality of life, and there was no effect on potentially-inappropriate medications.

Association of Lithium in Drinking Water With the Incidence of Dementia

Kessing, et al.

Studies have suggested that lithium, even at sub-therapeutic levels, may influence human cognition. This Danish nationwide study examined longitudinal data from geographically-specific drinking water measurements for all patients aged 50-90 years with a hospital contact and a diagnosis of dementia over 33 years. The distribution of lithium exposure was compared in patients with dementia and sex- and age-matched controls. Lithium exposure was nonlinearly associated with a diagnosis of dementia. Compared with individuals exposed to 2.0-5.0µg/L, those with an exposure of 10.1µg/L to >15.0µg/L had a decreased incidence rate ratio of dementia, however those with an exposure between 5.1-10.0µg/L had an increases incidence rate ratio. Similar patterns were found with Alzheimer's disease and vascular dementia. Thus, long-term increased lithium exposure in drinking water may be associated with lower incidence of dementia in a non-linear pattern; however, confounding factors could not be excluded.

Association of Antidepressant Medication Use During Pregnancy With Intellectual Disability in Offspring

Viktorin, et al.

This population-based cohort study of 179,007 children born between January 1, 2006 and December 31, 2007, and followed throughout 2014, examined the association between any maternal antidepressant medication use during pregnancy and intellectual disability (ID) in offspring. ID was diagnosed in 0.9% of children exposed to antidepressants in utero and in 0.5% of children who were unexposed to antidepressants. After adjusting for cofounders, the relative risk of ID after antidepressant exposure was statistically-insignificant at 1.33 in the full population sample. Thus, although there is no evidence of an association between ID and maternal antidepressant medication use during pregnancy, there may be an association between ID and other factors, such as parental age and mother's psychiatric disorder.

The Journal of Clinical Psychiatry

JCP Weekly – 09/05/17 – 09/19/17

Meta-Analysis of the Antidepressant Effects of Acute Sleep Deprivation

Boland, et al.

The objective of this meta-analysis was to provide a quantitative measure of the antidepressant effects of intentional sleep deprivation to complement qualitative reviews addressing response rates. The authors reviewed 66 independent studies. The overall response rate to sleep deprivation was 45% among studies that utilized a randomized control group and 50% among studies that did not. Partial sleep deprivation (sleep for three to four hours followed by forced wakefulness for 20-21 hours) did not significantly differ from total sleep deprivation (being deprived of sleep for 36 hours). There were also no significant differences with regards to the nature of the clinical sample, medication status, the definition of response used, or age and gender of the sample. Authors conclude that this warrants further investigation in this area.

Higher Baseline Proinflammatory Cytokines Mark Poor Antidepressant Response in Bipolar Disorder
Benedetti, et al.

Cytokines can influence neurotransmitters, neuroplasticity, and white matter integrity. Research has been inconsistent regarding higher cytokine levels link in hampering antidepressant response. The authors suggested value in studying total sleep deprivation (TSD) and light therapy (LT) as a treatment model to further investigate due to the rapid antidepressant response of TSD and LT. They studied at baseline 15 immune-regulating compounds in 37 consecutively admitted inpatients with a major depressive episode in the course of bipolar disorder compared to 24 controls. Patients were given 3 TSD and LT cycles in 1 week, with a 62% response rate (IDS-C score <12). In the nonresponder population there were higher levels of five highly intercorrelated compounds (IL-8, MCP-1, IFN- γ , IL-6, TNF- α). Additionally, higher body mass index correlated with higher cytokines. These proinflammatory compounds reflect an M1-like proinflammatory state of monocytes/macrophages and are associated with a poor response to antidepressant TSD + LT treatment in bipolar depression.

Determining if Borderline Personality Disorder and Bipolar Disorder Are Alternative Expressions of the Same Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions
De la Rosa, et al.

Exploratory factor analysis and confirmatory factor analysis were performed on 25 symptoms assessing depression, mania, and borderline personality disorder, using data from the National Epidemiologic Survey on Alcohol and Related Conditions, a large nationally representative sample of the US adult population (N = 34,653). Factor analyses identified depression, mania and borderline personality disorder as three separate factors based on DSM-IV symptoms. The correlations between the Borderline Personality Disorder and Depression factors ($r = 0.328$) and between the Borderline Personality Disorder and Mania factors ($r = 0.394$) were lower than the correlation between Depression and Mania factors ($r = 0.538$). The pattern of pairwise correlations between the 3 factors is consistent with the clinical presentation of 2 syndromes (depression and mania) that can be characterized as a unitary psychiatric entity (bipolar disorder) and a third syndrome (borderline personality disorder) that is often comorbid with bipolar disorder. The findings converge in suggesting that bipolar disorder and borderline personality disorder are overlapping but different pathologies.

The Lancet Psychiatry

Volume 4, Issue 10

The effects of improving sleep on mental health (OASIS): a randomized controlled trial with mediation analysis

Freeman, et al.

This single-blind, randomized controlled trial, conducted at 26 UK universities, aimed to determine whether treating insomnia leads to a reduction in subclinical paranoia and hallucinations in university students with insomnia. The researchers assigned 3755 participants to receive digital CBT for insomnia (n=1891) or usual practice (n=1864). Compared with the usual practice, the sleep intervention at 10 weeks reduced insomnia (effect size= 1.11; p<0.0001), paranoia (effect size=0.19; p<0.0001), and hallucinations (effect size=0.24; p<0.001); It appears that treating insomnia improves subclinical paranoia and hallucinations, but the effect sizes are small.

Functional connectivity of large-scale brain networks in patients with anti-NMDA receptor encephalitis: an observation study

Peer, et al.

This observational study aimed to understand how antibody-mediated NMDA receptor dysfunction leads to severe neuropsychiatric symptoms including psychosis, memory-deficits, and movement disorders. The researchers recruited 43 patients with anti-NMDAR encephalitis. Widespread alterations of functional connectivity that correlate with clinical measures were observed. These alterations included impaired hippocampal function connectivity, decoupling of the medial temporal and the default-mode networks, and an overall impairment of frontotemporal connections. Memory impairment correlated with hippocampal and medial-temporal-lobe network connectivity, whereas schizophrenia-like symptoms were associated with functional connectivity changes in frontoparietal networks. In machine-learning analyses frontoparietal and frontotemporal connections discriminated between patients and controls with an overall accuracy of 81%.

Journal of the American Academy of Child and Adolescent Psychiatry

Volume 56, Issue 10

A Randomized, Placebo-Controlled Trial of Metformin for the Treatment of Overweight Induced by Antipsychotic Medication in Young People With Autism Spectrum Disorder: Open-Label Extension

Handen, et al.

This 16-week open-label extension trial examined sustained improvement and adverse events in overweight youth with ASD on atypical antipsychotics placed on metformin. Participants (N=55) had initially participated in a double-blinded, randomized, placebo-controlled study of metformin for weight

stabilization in youth with ASD. All participants were titrated to a therapeutic dose of metformin (500mg or 850mg twice daily for ages 6-9 or 10-17). Subjects on metformin were continued on metformin, and those on placebo were switched to metformin during the open-label extension. Outcome measures used were Z-scores for BMI, body composition, and metabolic parameters. Subjects switched to metformin from placebo experienced improvement in BMI, body composition and HbA1C (~1 mmol/L) but not in other metabolic variables. Participants initially randomized to metformin maintained their BMI. GI distress was a primary adverse event, improved by meal-time dosing.

Randomized Clinical Trial of Dialectic Behavior Therapy for Preadolescent Children With Disruptive Mood Dysregulation Disorder: Feasibility and Outcomes

Perepletchikova, et al.

This randomized trial examined feasibility and preliminary efficacy of DBT adapted for preadolescent children (DBT-C) ages 7-12 with DMDD. Of 43 participants, 21 were randomized to DBT-C and 22 to treatment as usual (TAU). Therapists treating children in the TAU group were restricted from using DBT methods. Assessments were conducted at weeks 8, 16, 24, and 32 of treatment and again at 3-month follow-up. Feasibility was measured by recruitment, randomization, retention, attendance, satisfaction, and therapist adherence. Primary efficacy was measured using the CGI-Improvement scale and behavior/mood by the CGI-Severity scale. Positive response rates were 90.4% vs. 45.5% for DBT vs. TAU. Participants in DBT-C had remission rates of 52.4% as opposed to 27.3% for TAU.

Suicide Attempts in Juvenile Bipolar vs. Major Depressive Disorders: Systematic Review and Meta-Analysis

De Crescenzo, et al.

This meta-analysis used data from 6 studies of youth diagnosed with BD or MDD and history of at least one suicide attempt to assess risk of suicide in BD vs. MDD. Exclusion criteria included studies with undifferentiated inclusion of adult data, studies that did not include or differentiate BD and MDD, and studies without suicide attempt data. Rates of suicide attempt were ~5.2% in youth with mood disorders vs. 1.18% in healthy controls. Rates were twice as high among girls than boys. Youth with BD had 1.54 times the rate of at least one attempt as compared to youth with MDD (incident of 31.5% vs. 20.5%, respectively). Rate of attempt in hypomania or mania-only was 8.49%. Higher risk of suicide was associated with manic-depressive mixed states, marked by agitation, increased energy, and dysphoria.

Systematic Review of Universal Resilience-Focused Intervention Targeting Child and Adolescent Mental Health in the School Setting

Dray, et al.

This review assessed data from 57 RCT's, which utilized universal, school-based resilience-strengthening interventions to improve mental health outcomes in youth ages 5-18. Targeted outcomes were anxiety and depressive symptoms, hyperactivity, conduct problems, internalizing and externalizing problems,

and general psychological distress. Subgroup analysis was conducted for age (children 5-10 years vs. adolescents 11-18 years) and length of follow-up. For children, significant overall effect was found for anxiety and general psychological distress. For adolescents, significant overall effect was found for internalizing problems only. For short-term follow-up, interventions were effective for anxiety and depressive symptoms. For long-term follow-up, interventions were effective for internalizing problems.