Department of Psychiatry

RESEARCH WATCH

University Hospitals

December 2017 - Volume 3, Issue 12

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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)
* Acta Psychiatrica Scandinavica (APS)
* British Journal of Psychiatry (BJP)

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Highlights

- MIN-101 (5-HT2a and sigma2 antagonist) shows efficacy for negative symptoms of schizophrenia in phase 2 RCT. (AJP)
- RCT shows extended-release naltrexone to be as effective as buprenorphine-naloxone in maintaining short-term abstinence from heroin and other illicit substance use. (JAMA-P)
- PET study shows comparable elevations in dopamine synthesis capacity in both bipolar psychosis and schizophrenia, and positive association with psychosis severity. (JAMA-P)
- A large cohort study shows no evidence of significant change in self-rated personality prior to onset of mild cognitive impairment or clinical dementia. (JAMA-P)
- Results of 1-year KINECT 3 extension study suggest that long-term safety and tolerability of valbenazine are favorable with sustained treatment effect. (JCP)
- Population based cohort studies suggest an association between paternal depressive symptoms and depressive symptoms in their adolescent offspring. (LP)
- Study demonstrates that clinical subjects with psychotic disorders and non-clinical community subjects with psychotic experiences differ with regards to paranoid and threatening cognitive interpretations of their psychotic experiences. (LP)
- Lurasidone demonstrates efficacy and safety in children and adolescents with bipolar I depression in 6-week placebo-controlled study. (JAACAP)
- Traumatic exposure interacts with bipolar disorder genetic risk to increase risk of suicide attempts. (JAACAP)
- Neuroimaging study shows that young adults with borderline personality disorder show greater frontolimbic asymmetry in anterior cingulate cortex and anterior insula regions. (APS)
- A systematic review suggests that total and LDL cholesterol levels are reduced in first episode psychosis, while triglycerides are elevated. (BJP)

The American Journal of Psychiatry
Volume 174, Issue 12

PTSD Psychotherapy Outcome Predicted by Brain Activation During Emotional Reactivity and Regulation
Fonzo, et al.

This RCT aimed to identify baseline functional traits associated with positive treatment outcome in individuals with PTSD. Adults with PTSD (N=66) were recruited and randomized into well matched groups of immediate treatment with prolonged exposure therapy (N=36) and waitlist (N=30). Participants in each group completed pre- and post- intervention behavioral paradigms (measuring emotional reactivity, emotional conflict, gender conflict, and reappraisal) while undergoing fMRI. A subset of the immediate treatment group (N=17) also underwent single pulse TMS concurrent with fMRI to further explore brain circuitry. Primary outcome measure was PTSD symptoms as assessed by Clinician Administered PTSD Scale for DSM-IV (CAPS). Individuals in the immediate treatment group with greater symptom reductions showed more dorsal prefrontal activation and less left amygdala activation during the emotional reactivity task as compared to waitlist group at baseline. Those with more treatment related symptoms reductions also demonstrated better inhibition of left amygdala (induced by right DLPFC TMS pulses) and greater ventromedial prefrontal activation during emotional conflict regulation versus waitlist group at baseline.

Efficacy and Safety of MIN-101: A 12-Week Randomized Double-Blinded, Placebo-Controlled Trial of a New Drug in Development for the Treatment of Negative Symptoms in Schizophrenia
Davidson, et al.

This phase 2b multi-center RCT examined the efficacy, safety, and tolerability of MIN-101 (a 5-HT2a and sigma2 antagonist) compared to placebo in treating negative symptoms of schizophrenia. Adults diagnosed with schizophrenia (N=244) who were deemed psychiatrically stable and experienced moderately severe negative symptoms for at least 3 months prior were enrolled in the study. Patients were withdrawn from depot antipsychotics for 1 month prior and taken off oral antipsychotics for at least 5 days, and then randomized to receive MIN-101 32 mg or 64 mg daily or placebo for 12 weeks. Primary outcome measure was the negative factor score on the Positive and Negative Syndrome Scale (PANSS). All participants were Caucasian and 56% were male. There was a statistically significant difference in PANSS negative symptoms, with lower scores for MIN-101 32 mg/day and 64 mg/day groups compared to placebo group (effect sizes d=0.45 and d=0.57 respectively). Secondary outcomes supported these findings. There were no significant differences in PANSS positive scores or safety and tolerability measures in MIN-101 groups versus the placebo group.

JAMA Psychiatry
Volume 74, Issue 12

Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial
Tanum, et al.

A 12-week, multicenter, open-label randomized clinical trial was conducted at 5 urban addiction clinics in Norway to determine whether extended-release naltrexone is as effective as daily buprenorphine-naloxone to treat opioid dependence. A total of 232 opioid-dependent adults were randomized to receive daily buprenorphine-naloxone, 4 to 24mg daily, or intramuscular extended relief naltrexone hydrochloride 380 mg administered every fourth week. Primary outcome measures included RCT completion rate, proportion of opioid-negative urine drug tests, and number of days of heroin and other illicit opioids use. Among 159 participants, treatment with extended-release naltrexone showed noninferiority to daily buprenorphine-naloxone. Similarly, treatment with extended-release naltrexone showed noninferiority on group proportion of opioid-negative urine drug tests and use of heroin and other opioids. Superiority analysis showed significantly lower use of heroin and other illicit opioids in the extended-release naltrexone group.

A Test of the Transdiagnostic Dopamine Hypothesis of Psychosis Using Positron Emission Tomographic Imaging in Bipolar Affective Disorder and Schizophrenia
Jauhar, et al.

In order to test the hypothesis that dopamine abnormalities underlie psychosis, regardless of diagnosis, 60 individuals underwent positron emission tomography in this cross-sectional case-control study. In addition to 22 matched controls, 22 included patients had bipolar psychosis and 16 had schizophrenia - both groups being antipsychotic naive or free. Standardized clinical measures included the Positive and Negative Syndrome Scale, Young Mania Rating Scale, and the Global Assessment of Functioning. Dopamine synthesis capacity (Ki^{cer}) was significantly elevated in both the bipolar group and the schizophrenia group, as compared with the controls, and there were no significant differences between the bipolar and schizophrenia groups. Additionally, Ki^{cer} was significantly positively correlated with positive psychotic symptom severity in the combined sample experiencing a psychotic episode, explaining 27% of the variance in symptom severity. After adjusting for manic symptom severity in the bipolar group, this positive association remained significant.

Genetic Association of Major Depression With Atypical Features and Obesity-Related Immunometabolic Dysregulations
Milaneschi, et al.

This study sought to determine if the genetic overlap between major depression and increased body mass index (BMI) and higher levels of C-reactive protein (CRP) and leptin was stronger in those persons who experience increased appetite and/or weight during a depressive episode. Employing genotypic and phenotypic measures from 14 cohorts of European descent, 11,837 participants with major depressive

disorder were stratified into 3 subgroups using the DSM-IV appetite/weight (A/W) symptoms as "decreased", "increased" or no change. Common genetic variants explained 10% of the heritability in the subgroups. The increased A/W subgroup demonstrated a strong positive genetic correlation with BMI, while the decreased subgroup showed an inverse correlation. Furthermore, the decreased subgroup had a higher polygenic risk for increased BMI, CRP, and leptin. This indicates that phenotypic associations between atypical depressive symptoms and obesity-related measures may share a common pathophysiologic mechanism in patients with major depressive disorder.

Personality Change in the Preclinical Phase of Alzheimer Disease
Terracciano, et al.

A cohort of 2,046 community-dwelling older adults with no cognitive impairment at first assessment were followed up for up to 36 years (mean [SD], 12.05 [9.54] years) to determine whether increases in neuroticism, declines in conscientiousness, and changes in other personality traits occur before the onset of mild cognitive impairment or dementia. The change in self-rated personality traits were assessed with the Revised NEO Personality Inventory. Mild cognitive impairment was diagnosed in 104 (5.1%) individuals, and all-cause dementia was diagnosed in 255 (12.5%) participants, including 194 (9.5%) with Alzheimer disease. There were no significant differences in the rates of change of personality trajectory between the non-impaired and Alzheimer disease groups for neuroticism, conscientiousness, and the other personality traits. However, individuals who developed dementia scored significantly higher on neuroticism and significantly lower on conscientiousness and extraversion.

The Journal of Clinical Psychiatry
JCP Weekly - 11/14/17 - 12/05/17

Anticholinergic Burden and Cognition in Older Patients With Schizophrenia
Tsoutsoulas, et al.

This study investigated the risks associated with anticholinergic use in 60 community-dwelling patients aged ≥ 50 years with schizophrenia. The authors assessed the impact of anticholinergic burden on Alzheimer's dementia–related and schizophrenia-related cognitive functions in older patients with schizophrenia using the Anticholinergic Cognitive Burden scale (ACB) and the Cambridge Neuropsychological Test Automated Battery (CANTAB). Regression analyses were used to assess the relationships between anticholinergic burden and cognition. ACB scores were associated with spatial working ($P = .04$) and immediate ($P = .004$) memory and visuospatial ability ($P = .02$) and showed a trend toward association with impaired learning ($P = .06$), but were not associated with attention, executive function, language, or reaction time. An ACB cutoff score of ≤ 1.5 can detect cognitive impairment with a sensitivity of 90.3% and specificity of 48.3%. The ACB is a potentially useful screening tool that can help identify patients at risk of developing anticholinergic-related cognitive impairment.

Refining Prediction in Treatment-Resistant Depression: Results of Machine Learning Analyses in the TRD III Sample
Kautzky, et al.

The authors set out to create a prediction model for treatment-resistant depression (TRD) using machine learning featuring a large set of 47 clinical and sociodemographic predictors of treatment outcome. The population size was 552 patients with major depressive disorder. TRD was defined as failure to reach response to antidepressant treatment, characterized by a Montgomery-Asberg Depression Rating Scale (MADRS) score below 22 after at least 2 antidepressant trials of adequate length and dosage were administered. RandomForest (RF) was used for predicting treatment outcome phenotypes in a 10-fold cross-validation. Using the machine learning algorithm RF, an efficient prediction model with an accuracy of up to 75.0% for forecasting treatment outcome could be generated. This was determined to surpass the predictive capabilities of clinical evaluation.

The Effects of Valbenazine in Participants with Tardive Dyskinesia: Results of the 1-Year KINECT 3 Extension Study
Factor, et al.

Valbenazine is a highly selective vesicular monoamine transporter 2 inhibitor that is approved for the treatment of tardive dyskinesia. Participants from the KINECT 3 study with a diagnosis of schizophrenia, schizoaffective disorder, or a mood disorder were eligible to enter the 42-week valbenazine extension (VE) period and subsequent 4-week washout period. Of the 198 participants who entered the VE period, 124 (62.6%) completed treatment (week 48), and 121 (61.1%) completed the follow-up visit after washout (week 52). Efficacy assessments included the Abnormal Involuntary Movement Scale (AIMS) and Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD). AIMS and CGI-TD measures indicated sustained tardive dyskinesia improvement, with scores returning toward baseline after 4 weeks of valbenazine washout. Participants who received placebo and entered the VE period were re-randomized 1:1 to valbenazine 80 or 40 mg while others continued valbenazine at the KINECT 3 dose. A total of 15.7% of participants discontinued due to treatment-emergent adverse events. The long-term safety and tolerability of valbenazine were generally favorable, and maintenance of treatment effect was apparent with both doses during this long-term study.

The Lancet Psychiatry
Volume 4, Issue 12

The association between paternal and adolescent depressive symptoms: evidence from two population-based cohorts
Lewis, et al.

This study aimed to assess the association between paternal and adolescent depressive symptoms in two large population-based cohort studies. The researchers used data for two-parent families from two

representative prospective cohorts in Ireland (Growing up in Ireland [GUI] and the UK (Millennium Cohort Study [MCS]). There were 6070 families in GUI and 7768 in MCS. After all adjustments, a 1 SD (three-point) increase in paternal depressive symptoms was associated with an increase of 0.24 SMFQ (Short Mood and Feelings Questionnaire) points (95% CI 0.03-0.45; p=0.023) in the GUI cohort and 0.18 SMFQ points (0.01-0.36; p=0.041) in the MCS cohort. This association was independent of, and not different in magnitude to, the association between maternal and adolescent depressive symptoms. The results are suggestive of an association between depressive symptoms in fathers and depressive symptoms in their adolescent offspring.

Clinical relevance of appraisals of persistent psychotic experiences in people with and without a need for care: an experimental study
Peters, et al.

In Unusual Experiences Enquiry (UNIQUE) study, the researchers investigated the role of appraisals (the interpretations and meaning attributed to experiences) by comparing the individuals with persistent psychotic experiences without a need for care with patients and people without psychotic experiences. Eligible participants were patients with diagnosed psychotic disorders (clinical group) and adults in the general population with persistent psychotic experiences (non-clinical group) and without psychotic experiences (controls). The clinical group was more likely than the non-clinical group to display paranoid, personalizing interpretations of their psychotic experiences ($p<0.008$; p values were adjusted to account for multiple testing) and less likely to have normalizing ($p<0.008$) and supernatural ($p=0.039$) explanations. The clinical group also appraised their psychotic experiences as being more negative, dangerous, and abnormal and less controllable than the non-clinical group (all $p<0{\cdot}005$), but groups did not differ for attributions of general externality ($p=0{\cdot}44$). For experimentally induced anomalous experiences, the clinical group endorsed more threatening appraisals on all tasks than the non-clinical group ($p<0{\cdot}003$), who did not differ from the control group. The study provides evidence that psychotic experiences are appraised differently between clinical and non-clinical populations, supporting cognitive models of psychosis. It is possible that the absence of paranoid and threatening appraisals might protect against persistent psychotic experiences becoming clinically relevant.

Journal of the American Academy of Child and Adolescent Psychiatry Volume 56, Issue 12

Efficacy and Safety of Lurasidone in Children and Adolescents With Bipolar I Depression: A Double Blind, Placebo-Controlled Study
DelBello, et al.

This 6-week randomized, double-blind, placebo-controlled trial examined lurasidone treatment outcomes in youth 10-17 years old (N= 347) with BP-1 depression based on DM-5 criteria, Children's Depression Rating Scale-Revised (CDRS-R) score ≥45, and YMRS score ≤15. Lurasidone dosing ranged from 20-80 mg/day (mean: 32.5mg/day). Treatment response was defined as ≥50% symptom reduction

and remission as a CDRS-R score ≤28, YMRS ≤8, and CGI-BP-S depression score ≤3. Safety and tolerability were evaluated using SARS, AIMS, and BARS scores, physical exam and vital signs, laboratory studies, and 12-lead ECG. Treatment with lurasidone showed clinically significant LS mean change in CDRS-R and CGI-BP-S scores from baseline (-21.0 vs. -15.3 and -1.45 vs. -1.05, respectively) as well as improvement in anxiety symptoms, global functioning, and quality of life. The lurasidone group had higher rates of response and remission (59.5% vs. 36.5%, NNT=5 for response; 26.0% vs. 18.8%, NNT=14 for remission). There were no serious adverse events or statistically significant effects on weight, lipid profile, or QTc interval.

Targeted Family Intervention for Complex Cases of Pediatric Obsessive-Compulsive Disorder: A Randomized Controlled Trial
Peris, et al.

This study compared the efficacy of CBT with standard family intervention (ST) vs. positive family interaction therapy (PFIT) in the treatment of pediatric OCD. Youth ages 8-17 (N=62) with a diagnosis of OCD complicated by poor family functioning were randomized to one of two treatment arms (ST vs. PFIT). All participants received 12 weeks of exposure based CBT, however ST families participated in 30-minute post-session family meetings whereas PFIT families met every other week for 1 hour of joint therapy. Multiple interview schedules were used to assess improvement in OCD severity and functional impairment and family functioning. PFIT demonstrated higher rates of remission as compared to ST per CGI-I scores (58% vs. 27%, respectively) as well as greater reductions in functional impairment, symptom accommodation, and family conflict, and improvements in family cohesion. At 3-month follow-up, 94% of PFIT and 82% of ST participants retained responder status.

Traumatic Stress Interacts With Bipolar Disorder Genetic Risk to Increase Risk for Suicide Attempts
Wilcox, et al.

This study sought to assess whether or not adolescent offspring and relatives (ages 12-21) of adults with bipolar disorder (BP-1, BP-II, or schizoaffective disorder bipolar type) were at greater risk of suicidal ideation/attempt and self-harm behaviors versus controls, while examining contribution of demographic factors, traumatic stress exposure, lifetime mood/substance use disorders, and BD polygenic risk score. Data for suicidal ideation, suicide attempts, and non-suicidal self-injury (NSSI) in 307 adolescent BD-relatives of adults with BD were compared to 166 matched controls (N=166). Peripheral blood samples were obtained for genotyping and BD-associated single nucleotide polymorphisms were selected based on prior evidence of genetic association from the PGC1-BD discovery sample. BD-relatives were 30% more likely to have ideation and attempts vs. controls (OR 1.3 vs. OR 1.3, respectively) but not NSSI. BD polygenic risk score by itself was marginally associated with attempts (p=.061). Independent of BD-relative versus control status, exposure to trauma within the past year (including bullying, sexual abuse, and domestic violence) was associated with suicide attempts (p=0.014). Notably the interaction between BD polygenic risk score and traumatic event exposures was significantly associated with suicide attempts (p=0.041) regardless of other characteristics, particularly in Caucasian-only analysis (OR=89.4, p=0.43).

Acta Psychiatrica Scandinavica
Volume 136, Issue 6

Hemispheric asymmetry of the frontolimbic cortex in young adults with borderline personality disorder
Zhou, et al.

This cross-sectional study examined frontolimbic cortex asymmetries in individuals with borderline personality disorder (BPD) as compared with healthy controls. Individuals 20-30 years old who were recruited from outpatient clinics and were diagnosed with BPD by two independent psychiatrists using the SCID-II/P were included (N=34 right handed) and compared to matched healthy controls (N=32 right handed). Exclusion criteria included comorbid psychiatric illness. Participants completed assessments of depression, impulsivity, affect intensity, childhood trauma, attachment style, and BPD symptoms. Participants also underwent MRIs and morphometric parameters of the frontolimbic cortex were extracted using FreeSurfer software. Results demonstrated that, as compared to healthy controls, patients with BPD had thinner left anterior cingulate cortex (ACC) thickness and less surface area and gray matter volume in the left anterior insula (AI). BPD patients showed greater frontolimbic asymmetry and asymmetry of ACC and AI was associated with a higher attention subscale score on the Barratt Impulsiveness Scale.

British Journal of Psychiatry
Volume 211, Issue 6

Cholesterol and triglyceride levels in first-episode psychosis: a systematic review and meta-analysis
Pillinger, et al.

A systematic review and meta-analysis was conducted to assess whether individuals with first-episode psychosis (FEP) and no or minimal antipsychotic exposure show lipid and adipocytokine abnormalities compared with healthy controls. Twenty case-control studies met inclusion criteria, including 1,167 patients and 1,184 controls. Total cholesterol levels were significantly decreased in patients compared with controls (g = −0.19, 95% CI −0.32 to −0.06; P = 0.005), corresponding to an absolute reduction of 0.26 mmol/L. LDL cholesterol was also significantly decreased in patients compared with controls (g = −0.22, 95% CI −0.35 to −0.09; P = 0.001), corresponding to an absolute reduction of 0.15 mmol/L. Triglyceride levels were significantly increased in the patient group (g = 0.14, 95% CI 0.00–0.28; P < 0.05), corresponding to an absolute increase of 0.08 mmol/L. However, HDL cholesterol and leptin levels were not significantly different in patients compared with controls.

Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies

Lally, et al.

The authors sought to assess pooled prevalence rates of remission and recovery in first-episode psychosis (FEP) in longitudinal studies with more than 1 year of follow-up. Seventy-nine studies were included representing 19,072 patients with first-episode psychosis. Among the 60 studies with data on remission (operationalized as improvement in symptoms for at least 6 months), the pooled rate of remission among 12,301 individuals with first-episode psychosis was 58% (mean follow-up 5.5 years, interquartile range 2.0-7.0). Higher remission rates were moderated by studies from more recent years. Among the 35 studies with data on recovery (operationalized as sustained improvement for >2 years in clinical and functioning dimensions), the pooled prevalence of recovery among 9,642 individuals with first-episode psychosis was 38% (mean follow-up 7.2 years, interquartile range 2.0-10.0). Recovery rates were higher in North America than in other regions, and higher recovery rates were moderated by white ethnicity.