

July 2018 - Volume 4, Issue 6

Chief Curator: Erin C. Fulchiero

Assistant Curators:

Shanna Swaringen
Javier Ponce Terashima

Curators:

Prakash Mishra
Rob Siedler
Heather Wobbe

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)
- * Misc: JAMA

Contact:

erin.fulchiero@uhhospitals.org

Highlights

- A phase 2 trial of intranasal esketamine plus standard-of-care treatment shows decreased suicidal ideation relative to placebo and antidepressant treatment at 4 and 24 hours but not at study endpoint. (AJP)
- A retrospective study shows that medication-assisted treatment (MAT) for alcohol use disorder in incarcerated individuals with serious mental illness improves psychotropic adherence and decreases emergency department visits and psychiatric hospitalizations during the 12 months following treatment. (AJP)
- A cross-sectional epidemiological study shows no significant association between urban residence and psychosis in low- and middle-income countries. (JAMA-P)
- Modeling analysis shows that offering ECT as a third-line treatment is cost-effective, reducing time with uncontrolled depression. (JAMA-P)
- Adjunctive treatment with standardized extract of the anti-inflammatory medicinal herb, *Withania somnifera*, has benefit in exacerbation of negative schizophrenia symptoms. (JCP)
- Adjunctive treatment with the anti-inflammatory medicinal herb, *Withania somnifera*, shows benefit for patients with schizophrenia experiencing exacerbation of negative and stress symptoms. (JCP)
- RCT shows that CBT did not have a lasting effect on total symptoms of schizophrenia compared with treatment as usual. (LP)
- Individuals with long-standing fear of heights improved substantially with a virtual reality program without a therapist. (LP)
- Meta-analysis of six register-based and clinical cohort studies shows an increased risk for neonatal readmission major malformations but not for cardiac malformations in lithium-exposed pregnancies. (LP)
- Frequent checking, posting, browsing, streaming, and other online activity is associated with higher likelihood of meeting ADHD criteria 2 years later. (JAMA)

The American Journal of Psychiatry

Volume 175, Issue 7

Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study

Canuso, et al.

In this initial double-blind, multicenter, proof-of-concept study, authors compared standard-of-care treatment plus intranasal esketamine versus placebo for rapid reduction of suicidality among depressed individuals at imminent suicide risk. A total of 68 patients were assigned to receive esketamine (84 mg) or placebo twice weekly for one month, in addition to standard antidepressant treatment. Change in MADRS score from baseline to 4 hours after initial dose was assessed, as was clinician global judgment of suicide risk. Both measures were evaluated also at 24 hours and day 25. Overall, a significantly greater improvement in MADRS score was observed in the esketamine group compared with placebo at 4 hours (least-square mean difference=-5.3, SE=2.10; effect size=0.61) and at ~24 hours (least-square mean difference=-7.2; SE=2.85; effective size=0.65) but not at day 25. Significantly greater improvement was also noted in the esketamine group on the MADRS suicidal thought item score at 4 hours, but not at 24 hours or at day 25. Clinician global judgment of suicide risk scores were not statistically different at any time point.

Sensitization of the Neural Salience Network to Repeated Emotional Stimuli Following Initial Habituation in Patients with Borderline Personality Disorder

Denny, et al.

Borderline personality disorder (BPD) has been attributed to two mechanisms of response to negative stimuli: impairment in habituation and exaggerated sensitization of activity in the neural salience network, including the amygdala, anterior insula, and dorsal cingulate cortex. The authors sought to distinguish between these theories in this longitudinal neuroimaging study. Repeated negative emotional and neutral images were shown to adults with BPD, healthy adult controls, and a psychiatric control group of adults with avoidant personality disorder. Images of negative and neutral social interactions were shown 5 times each during two sessions 3 days apart. Behavioral responses were measured by self-reports of negative affect, as well as activity in the neural regions subserving emotional, interoceptive processing and directed attentional processes. While all participants showed habituation of salience network neural activity within each session in response to negative emotional images, only the BPD group showed increased activity between sessions. Less habituation of self-reported negative affect in the BPD group versus controls nearly reached statistical significance. Abnormal sensitization was also evident for neutral images in the BPD group, suggesting that individuals with the disorder may perceive negativity in, and sensitize to, otherwise neutral social situations.

Medication-Assisted Treatment for Alcohol-Dependent Adults With Serious Mental Illness and Criminal Justice Involvement: Effects on Treatment Utilization and Outcomes

Robertson, et al.

The authors examined the effects of medication-assisted treatment (MAT) for alcohol use disorder (acamprosate, disulfiram, naltrexone) on long-term mental health treatment utilization and criminal justice outcomes among adults with history of incarceration, serious mental illness and alcohol use disorder. Data were merged from public agencies in Connecticut for 5,473 adults with schizophrenia spectrum disorder, bipolar disorder, or major depressive disorder comorbid with moderate to severe alcohol dependence and incarceration for at least one night during 2002-2009. Longitudinal multivariable regression models were used to estimate the effect of MAT compared with other outpatient substance abuse treatments on inpatient hospitalizations, emergency department visits, criminal convictions and incarcerations. MAT was associated with significant improvement in clinical outcomes in the year following initiation compared with non-MAT treatment, including greater reductions in psychiatric hospitalization and ED visits, as well as improved psychotropic medication adherence. No benefits were identified for criminal justice outcomes with the exception of significant reductions in felony convictions among adults with bipolar disorder.

JAMA Psychiatry

Volume 75, Issue 7

Association of Urbanicity With Psychosis in Low- and Middle-Income Countries

DeVylder, et al.

Using World Health Survey data from 215,682 adults residing in 42 low- and middle-income countries, the authors conducted this cross-sectional epidemiological study to evaluate the association between psychosis and urban residence. Psychotic experiences were assessed using the WHO Composite International Diagnostic Interview psychosis screen, and self-reported lifetime history. In contrast to prior studies evaluating only high-income countries, pooled analyses and meta-analyses suggest that urban residence was not significantly associated with psychotic experiences (OR, 0.97; 95% CI, 0.87-1.07) or psychotic disorder (OR, 0.92; 95% CI, 0.73-1.16) in either low- or middle-income countries. These results indicate that urbanicity may be a risk factor for psychosis in high-income countries only.

Association of Daily Intellectual Activities With Lower Risk of Incident Dementia Among Older Chinese Adults

Lee, et al.

This longitudinal observational study of 15,582 community-living older Chinese individuals examined whether late-life participation in intellectual activities is associated with a lower risk of incident dementia, independent of other lifestyle and health-related factors. Comprehensive cognitive evaluations were conducted at baseline and throughout follow-up, with diagnosis of dementia made in

accordance with the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, or a Clinical Dementia Rating of 1 to 3. The study found a significantly lower risk of incident dementia during 5 years of median follow-up among individuals with intellectual activities at baseline with estimated odds ratio 0.71 (95% CI, 0.60-0.84, P<.001).

Cost-effectiveness of Electroconvulsive Therapy vs Pharmacotherapy/Psychotherapy for Treatment-Resistant Depression in the United States

Ross, et al.

Using input data from meta-analyses, randomized trials, and observational studies, Ross and colleagues developed a decision analytic model to evaluate the cost-effectiveness of electroconvulsive therapy (ECT) compared with antidepressant medications and/or psychotherapy for treatment-resistant depression. They found that ECT offered for treatment-resistant depression after failure of 2 or more trials of pharmacotherapy/psychotherapy was cost-effective and was projected to reduce time with uncontrolled depression from 50% of life-years to 33% to 37% over a 4-year period.

Association of Depressive Symptoms and Heart Rate Variability in Vietnam War-Era Twins: A Longitudinal Twin Difference Study

Huang, et al.

In this longitudinal twin difference study, 146 twins (73 pairs) who served in the US Military during the Vietnam War and were discordant for depression were recruited from the Vietnam Era Twin Registry. Baseline assessments were performed from March 2002 to March 2006 with a 7-year follow-up visit at an academic research center. At both visits, depressive symptoms were measured using the Beck Depression Inventory-II (BDI-II). Heart rate variability (HRV), an index of autonomic dysregulation, was measured through 24-hour EKG monitoring. Results showed that lower HRV at baseline is independently associated with increasing depressive symptoms at follow-up. However, the relationship between depressive symptoms at baseline and lower heart rate variability at follow-up was mostly explained by antidepressant medication use. Findings suggest that autonomous nervous system dysregulation may be a risk factor for the development of depression.

The Journal of Clinical Psychiatry

Volume 79, Issue 4

Appetitive Symptoms Differentially Predict Treatment Response to Fluoxetine, Light, and Placebo in Nonseasonal Major Depression

Levitan, et al.

Secondary analysis of data from a randomized, double-blind study conducted in 3 psychiatric outpatient clinics in Vancouver and Toronto examined whether appetitive symptoms predict response to bright light therapy in nonseasonal MDD patients. In 122 patients who met DSM-IV-TR criteria for MDD

without a seasonal pattern were randomly assigned to light monotherapy, fluoxetine, combination light and fluoxetine, or double-placebo (inactivated negative ion generator plus placebo pill). Multiple regression assessed the percentage change in the Montgomery-Asberg Depression Rating Scale (MADRS) scores based on treatment condition, appetite symptom score at baseline (sum of 4 items on the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version), and the condition-by-appetitive score interaction. For individuals in the placebo group, more appetitive symptoms at baseline predicted less decrease in MADRS scores at 8 weeks ($r=-0.37$; large effect size). In contrast, for individuals in the active treatment groups, more appetitive symptoms at baseline predicted more of a decrease in depression scores at 8 weeks (fluoxetine group $r = +0.23$, medium effect size; light therapy group $r = +0.11$, small effect size; combination group $r = +0.32$, medium to large effect size).

Adjunctive Use of a Standardized Extract of *Withania somnifera* (Ashwagandha) to Treat Symptom Exacerbation in Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study

Chengappa, et al.

The immune-inflammatory dysregulation theory in schizophrenia posits an imbalance in pro- and anti-inflammatory cytokines and elevated levels of inflammatory proteins in subgroups of patients with schizophrenia experiencing exacerbation of symptoms. This randomized, controlled trial sought to determine whether adjunctive treatment with a standardized extract of *Withania somnifera* (WSE), a medicinal herb with immunomodulatory and anti-inflammatory actions, would prove beneficial for recently exacerbated symptoms in patients with schizophrenia. Sixty-six randomized patients experiencing an acute exacerbation of symptoms were assigned to receive WSE (1,000 mg/d) or placebo for 12 weeks, in addition to their antipsychotic regimen. Primary outcomes included change from baseline to end of treatment on the Positive and Negative Syndrome Scale (PANSS) between treatment groups. Secondary outcomes evaluated stress and inflammation using the Perceived Stress Scale (PSS), S100 calcium-binding protein B, and CRP. Beginning at 4 weeks and continuing to end of treatment, WSE produced significantly greater reductions in PANSS negative, general and total symptoms (Cohen d: 0.83, 0.76, 0.83), but not positive symptoms. PSS scores improved significantly with WSE versus placebo (Cohen d: 0.58).

The Lancet Psychiatry

Volume 5, Issue 8

Cognitive behavioural therapy in clozapine-resistant schizophrenia (FOCUS): an assessor-blinded, randomized controlled trial

Morrison, et al.

This RCT aimed to determine whether cognitive behavioral therapy (CBT) is an effective treatment for clozapine-resistant schizophrenia. The authors conducted a pragmatic, parallel group, assessor-blinded, randomized controlled trial in community-based and inpatient mental health services in five sites in the

UK. A total of 487 patients with schizophrenia who were intolerant or unresponsive to clozapine were randomly assigned to either CBT (n=242) plus treatment as usual or treatment as usual alone (n=245). The primary outcome was the Positive and Negative Syndrome Scale (PANSS) total score at 21 months and at end of treatment (9 months). Intention to treat analysis was performed on 209 in the CBT group and 216 in the treatment as usual group. No between-group differences occurred in the primary outcome (PANSS total at 21 months, mean difference -0.89, 95% CI -3.32 to 1.55, p=0.48), although the CBT group improved at the end of treatment (PANSS total at 9 months, mean difference -2.40, -4.79 to -0.02; p=0.049).

Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies

Munk-Olsen, et al.

This meta-analysis sought to investigate the association between in-utero lithium exposure and risk of pregnancy complications, delivery outcomes, neonatal morbidity, and congenital malformations. Primary data from pregnant women and their children from six international cohorts based in the community (Denmark, Sweden, and Ontario, Canada) and in the clinics (the Netherlands, UK, and USA) were analyzed. Pregnancies were included for study if they resulted in a liveborn singleton between 1997 and 2015, if health-related information was available for both mother and infant, and if the mother had a mood disorder or had been given lithium during pregnancy. Pregnancies were grouped into lithium-exposed group and a mood disorder reference group. Among 22,124 pregnancies, 727 were eligible for the lithium-exposed group. Among these, exposure was not associated with any of the predefined pregnancy complications or delivery outcomes. An increased risk for neonatal readmission within 28 days of birth was seen in the lithium-exposed group compared with the reference group (pooled prevalence 27.5% [95% CI 15.8-39.1] vs 14.3% [10.4-18.2]; pooled aOR 1.62, 95% CI 1.12-2.33). Lithium exposure during the first trimester was associated with an increased risk of major malformations (pooled aOR 1.71, 95% CI 1.07-2.72), but was not significantly associated with major cardiac malformations (1.54, 0.64-3.70).

Second-generation antipsychotic drugs and short-term mortality: a systematic review and meta-analysis of placebo-controlled randomized trials

Schneider-Thoma, et al.

This systematic review and meta-analysis aimed to assess the contribution of antipsychotic side-effects to reduced life expectancy in individuals with severe mental disorders. A total of 352 studies (comprising 84, 988 participants) with mortality data available constituted the main data set for meta-analysis. Overall, 207 (0.4%) deaths were reported in 53,804 patients on an antipsychotic drug versus 99 (0.3%) deaths in those on placebo. There was no evidence of a difference between antipsychotic drugs and placebo in mortality by any cause (OR 1.19; 95% CI 0.93-1.53), from natural causes (1.29; 0.85-1.94), from suicide (1.15; 0.47-2.81), and from other non-natural causes (1.55; 0.66-3.63). Most subgroup and meta-regression analyses did not indicate any important effect moderators. The exceptions were increased mortality in patients with dementia (OR 1.56; 95% CI 1.10-2.21), in elderly patients (1.38;

1.01–1.89), in aripiprazole-treated patients (2.20; 1.00–4.86), and in studies with a higher proportion of women (regression coefficient 0.025; 95% credible interval 0.010–0.040). For patients with schizophrenia, there was no evidence of an increased mortality risk (OR 0.69; 95% CI 0.35–1.35).

Automated psychological therapy using immersive virtual reality for treatment of fear of heights: A single-blind, parallel-group, randomised controlled trial

Freeman, et al.

Authors sought to evaluate the efficacy of an automated cognitive intervention for fear of heights guided by an avatar virtual coach in virtual reality (VR). The RCT compared a VR program with an automatic coaching feature with usual care in 100 individuals with long-standing fear of heights (mean duration, 30 years). Fear of heights was diagnosed using the Heights Interpretation Questionnaire (HIQ), a 16-item self-report scale. Participants were allocated to usual care or to program involving six 30-minute sessions over 2 weeks. Randomization was stratified by severity of fear of heights. Programming provided gradual exposure to heights but emphasized testing patient-rated cognitive expectations rather than requiring exposure until anxiety was reduced. Attempts were made to eliminate safety-seeking behaviors that might interfere with exposure effects. Overall, VR uptake was extremely high with 47 (96%) of 49 enrollees attending at least one session and 90% completing treatment. At study end, 69% of the VR group no longer had height phobia, and 78% had a $\geq 50\%$ improvement, compared with none in usual care. Number needed to treat to at least halve fear of heights was 1.3. Of note, the study was partly funded by the manufacturer, which employed several authors.

Journal of the American Academy of Child and Adolescent Psychiatry

Volume 57, Issue 7

Results from the Child/Adolescent Anxiety Multimodal Extended Long-Term Study (CAMELS): Primary Anxiety Outcomes

Ginsburg, et al.

Pediatric anxiety disorders are highly prevalent, associated with severe disability, and confer high personal and economic costs. Researchers reported anxiety outcomes from the Child/Adolescent Anxiety Multi-modal Extended Long-term Study (CAMELS), a five-year follow-up study of anxious youth ($n = 319$) enrolled in the landmark RCT, Child/Adolescent Anxiety Multimodal Study (CAMS). The study examined rates of stable anxiety remission (defined rigorously as the absence of all *DSM-IV TR* anxiety disorders across all follow-up years) and predictors of anxiety remission across a 4-year period, beginning 4 to 12 years after randomization to 12 weeks of SSRI, cognitive behavioral therapy (CBT), their combination, or pill placebo. Acute treatment response, treatment assignment, baseline child and family variables, and interim negative life events were assessed as predictors of remission. Results showed 21.7% of youth in stable remission, 30% with chronic illness, and 48% with relapse. Acute treatment responders were likely to be in the chronically ill group (odds ratio = 2.73; confidence interval = 1.14-6.54; $p < .02$). Several variables were identified as predictive of stable remission, including gender

and age at start of treatment. No association between treatment assigned and remission status over time was identified.

Cognitive-Behavioral Therapy for Children With Anxiety and Comorbid Attention-Deficit/Hyperactivity Disorder

Gould et al.

Authors examined the question of whether CBT for child anxiety is an appropriate treatment for children with comorbid anxiety and ADHD. A total of 842 children 5 to 18 years of age received group-based CBT with parent involvement. A subsample of 94 children met criteria for comorbid mild to moderate ADHD, including 61 children with predominantly inattentive type, 27 children with combined type, and two children classified with predominantly hyperactive type. Children with severely disabling ADHD or primary diagnosis of ADHD were excluded. Child participants accompanied by at least one parent received 9 to 12 sessions of the Cool Kids treatment program, an empirically supported manualized family-based CBT treatment delivered to groups of 4 to 6 children, including psychoeducation, cognitive restructuring, and therapeutic exposures sessions. Sessions involved group meetings with children and parents, time spent in child-only and parent-only groups, followed by meeting with children and parents together. The authors analyzed change in diagnostic severity (response) at post-treatment and 3- and/or 6-month follow-up according to the Anxiety Disorders Interview Schedule for Children. Results indicated no significant differences in response or remission between children with or without comorbid ADHD regardless of subtype. Additionally, children with comorbid ADHD demonstrated modest, significant improvements in ADHD severity ratings.

Miscellaneous

JAMA

Volume 320, Issue 3

Association of digital media use with subsequent symptoms of attention-deficit/hyperactivity disorder among adolescents

Ra, et al.

Researchers surveyed over 2500 students aged 15 to 16 years from 10 urban high schools over the course of 2 years. Teenagers had no ADHD diagnosis at baseline, but high-frequency media use (e.g., checking social media, video chatting, liking or commenting on others' posts, online browsing, or watching videos "many times per day") predicted new ADHD symptoms over time. For example, in teens reporting high frequency of all 14 media activities at baseline, almost 15% met ADHD criteria at follow-up, while in those reporting no high-frequency media use, only 4% met ADHD symptom criteria at follow-up.