



*Department of Psychiatry*  
**RESEARCH WATCH**



February 2018 - Volume 4, Issue 2

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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)

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**Highlights**

- Methylphenidate shows improvement in apathy in veterans with mild Alzheimer's disease in a placebo-controlled trial. (AJP)
- Adjunctive bright light therapy and transcranial direct current stimulation demonstrate efficacy for bipolar depression in RCTs. (AJP & JAMA-P)
- Study suggests 95% subjects screening positive for late-onset ADHD do not meet criteria for a valid ADHD diagnosis, with substance-induced cognitive impairment being the most common scenario. (AJP)
- Meta-analysis shows ketamine rapidly reduces suicidal thoughts within 1 day and for up to 1 week in depressed patients. (AJP)
- Phase 2 RCT suggests varenicline may have a role in the treatment of alcohol use disorder among men (but not women) who smoke cigarettes. (JAMA-P)
- RCT suggests efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in initially euthymic perimenopausal and early postmenopausal women. (JAMA-P)
- Intranasal esketamine demonstrates rapid and persistent efficacy for treatment resistant depression in phase 2 RCT. (JAMA-P)
- Congruent and incongruent facial emotion intensity rating robustly differentiates between behavioral variant frontotemporal dementia and major depressive disorder. (JCP)
- Swedish twin study suggests genetic association between autism spectrum phenotype and atypical sensory reactivity. (JAACAP)
- Longitudinal neuroimaging provides evidence of differences in uncinate fasciculus white matter structural development in adolescents and young adults with bipolar disorder compared to healthy controls. (JAACAP)
- Meta-analysis shows subjects with unipolar psychotic depression are at a two-fold higher acute and lifetime risk of suicide attempt compared to subjects with non-psychotic depression. (APS)
- Study shows a significant proportion of patients with schizophrenia considered treatment-resistant have subtherapeutic antipsychotic plasma levels. (APS)

**The American Journal of Psychiatry**  
**Volume 175, Issue 2**

**Adjunctive Bright Light Therapy for Bipolar Depression: A Randomized Double-Blind Placebo-Controlled Trial**

Sit, et al.

This 6-week RCT investigated the efficacy of bright light therapy at midday for treatment of bipolar depression. Adult patients (N=46) with bipolar I or II and concurrent moderate to severe depression without current or recent mania or hypomania and on stable psychotropic medications were assessed. Participants were assigned to receive either the active treatment 7000 lux bright light therapy (N=23) or the placebo 50 lux dim red light (N=23) at midday. Outcome measures were assessed on a weekly basis and included remission rate (using Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement, SIGH-ADS), symptom response rate, mood polarity switch, and sleep quality. Findings showed that the active treatment group had significantly higher remission rates at weeks 4-6 (68.2% vs. 22.2%, adjusted OR=12.6), lower mean depression scores at end point visit (9.6 vs. 14.9). No mood polarity switches were observed in either group and the groups both showed improvements in sleep quality with no significant differences.

**Late-Onset ADHD Reconsidered With Comprehensive Repeated Assessments Between Ages 10 and 25**  
Sibley, et al.

Researchers utilized data from the local normative comparison group of the Multimodal Treatment of ADHD in order to carefully investigate symptoms of late-onset ADHD longitudinally. A comparison subsample was identified (N=239) of individuals who did not meet diagnostic criteria for ADHD during childhood baseline assessment and who had completed at least one assessment in adolescence and in adulthood. Multi-informant assessments were completed measuring ADHD symptoms, impairment, substance use, and other mental disorders at each time point. Assessments were evaluated in a stepped diagnostic procedure to determine validity of cases that were initially classified as late-onset ADHD. Results indicated that approximately 95% of cases who originally screened positive for late-onset ADHD were excluded from this diagnosis as the symptoms or impairment occurred most commonly in the context of heavy substance use. Of those who were diagnosed as late-onset ADHD, most occurred in and were limited to adolescence and there was no evidence of adult-onset ADHD independent of a complex psychiatric history.

**The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis**

Wilkinson, et al.

Authors assessed the effect of ketamine on suicidal ideation through this systematic review and meta-analysis. A MEDLINE search was conducted using specific pertinent terms for articles published between

Jan. 1 2000 and Nov. 15, 2016. Only studies yielding single-dose IV ketamine compared to a control group (using saline or midazolam) in patients who had baseline suicidal ideation were included. Authors were contacted for patient level data (10 studies, N=167). The meta-analysis used a mixed-effects, multi-level, general linear model. Primary outcome measures were suicide items from clinician administered assessments (MADRS and HAM-D) and self-report scales (QIDS-SR and BDI). Ketamine significantly and more rapidly reduced suicidal ideation as assessed through clinician administered and self-report measures in comparison to control treatments throughout each point from dosing. There was a moderate to large effect size (Cohen's  $d=0.48-0.85$ ) at each point. There were significant benefits of ketamine on individual suicide items on the MADRS, HAM-D, QIDS-SR, but not on BDI. Even after adjusting for depression severity, ketamine's effect on suicidality remained significant.

### **Methylphenidate for Apathy in Community-Dwelling Older Veterans With Mild Alzheimer's Disease: A Double-Blind, Randomized, Placebo-Controlled Trial**

Padala, et al.

Apathy affects many patients with Alzheimer's disease, causing functional impairment, higher service utilization, higher caregiver burden, and increased mortality. This 12-week, prospective, double-blind, randomized, placebo-controlled trial (methylphenidate versus placebo) was conducted in community-dwelling male veterans (N=60) with mild Alzheimer's disease. Apathy, cognition, functional status, improvement and severity, caregiver burden, and depression were measured at 4, 8, and 12 weeks using various scales. The methylphenidate group had significantly greater improvement in apathy than the placebo group at 4 weeks, 8 weeks, and 12 weeks. There was a 9.9 point mean difference between methylphenidate and placebo on Apathy Evaluation Scale-Clinician at 12 weeks ( $p<0.001$ ). At 12 weeks, there was also greater improvement in cognition, functional status, caregiver burden, improvement and severity, and depression in the methylphenidate group compared with the placebo group.

## **JAMA Psychiatry**

### **Volume 75, Issue 2**

### **Effect of Varenicline Combined With Medical Management on Alcohol Use Disorder With Comorbid Cigarette Smoking: A Randomized Clinical Trial**

O'Malley, et al

A phase 2, randomized, double-blind, placebo-controlled trial was conducted to assess the effect of Varenicline combined with Medical Management on Alcohol Use Disorder with comorbid Cigarette Smoking. The study included 131 adult participants with alcohol-dependence (DSM-IV-TR criteria), with reported heavy drinking  $\geq 2$  times/week for the previous 90 days and smoking  $\geq 2$  times/week. A Heavy drinking day was defined as consuming  $\geq 5$  (for men) and  $\geq 4$  (for women) standard drinks containing 14 g of ethanol. Participants were randomized to either varenicline (1 mg BID) or placebo for 16 weeks, stratified by sex and site. Outcomes were Percentage of heavy drinking days (PHDD), no heavy drinking days (NHDD) which were calculated over the last 8 weeks of treatment (weeks 9 to 16), and prolonged

smoking abstinence, calculated over the last 4 weeks. Mean change in PHDD between varenicline and placebo was not significantly different. Stratified by sex, in the varenicline group, 13 of 45 men (29%) had NHDD compared with 3 of 47 men (6%) taking placebo (Cohen  $h = 0.64$ ; 95% CI, 0.22-1.03). Whereas 1 of 19 women (5%) had NHDD taking varenicline compared with 5 of 20 women (25%) taking placebo (Cohen  $h = -0.60$ ; 95% CI,  $-1.21$  to 0.04). Prolonged smoking abstinence was achieved in 8 of 64 participants (13%) in the varenicline group, compared with 0 of 67 in the placebo group ( $P = .003$ ; Cohen  $h = 0.72$ ; 95% CI, 0.38-1.07).

### **Efficacy and Safety of Transcranial Direct Current Stimulation as an Add-on Treatment for Bipolar Depression: A Randomized Clinical Trial**

Sampaio-Junior, et al

A randomized, sham-controlled, double-blind trial was conducted to assess the efficacy and safety of transcranial direct current stimulation (tDCS) as an add-on treatment for bipolar depression. Participants included 59 adults with type I or II bipolar disorder in a major depressive episode, receiving a stable pharmacologic regimen, with scores  $>17$  in the 17-item Hamilton Depression Rating Scale (HDRS-17), and with low suicide risk. The only psychiatric comorbidities allowed were anxiety disorders. Participants received daily 30-minute, anodal-left and cathodal-right prefrontal sessions of active or sham tDCS on weekdays and then 1 session every fortnight until week 6. Patients in the active tDCS group showed significantly superior improvement compared with those receiving sham in HDRS-17 scores at week 6 ( $\beta_{int} = -1.68$ ; NNT 5.8; 95% CI, 3.3-25.8;  $P = .01$ ). Sustained response was seen in 19 patients of the active group and in 8 of the sham group. Cumulative response rates were higher in the active vs sham groups (67.6% vs 30.4%; NNT 2.69; 95% CI, 1.84-4.99;  $P = .01$ ), but not remission rates (37.4% vs 19.1%; NNT 5.46; 95% CI, 3.38-14.2;  $P = .18$ ). Adverse events, including treatment-emergent affective switches, were similar between groups, except for localized skin redness that was higher in the active group (54% vs 19%;  $P = .01$ ).

### **Efficacy of Transdermal Estradiol and Micronized Progesterone in the Prevention of Depressive Symptoms in the Menopause Transition: A Randomized Clinical Trial**

Gordon, et al

A double-blind, placebo-controlled randomized trial was conducted to assess the efficacy of transdermal estradiol plus intermittent micronized progesterone (TE+IMP) in preventing depressive symptom onset among initially euthymic perimenopausal and early postmenopausal women (aged 45 to 60 years). Depressive symptoms were assessed at each study visit (baseline and months 1, 2, 4, 6, 8, 10, and 12) using the Center for Epidemiologic Studies–Depression Scale (CES-D), with clinically significant depressive symptoms defined as a score  $\geq 16$ . Of 172 participants, 43 developed clinically significant depressive symptoms. Women assigned to placebo were more likely than those assigned to TE+IMP to score  $\geq 16$  on the CES-D at least once during the intervention phase (32.3% vs 17.3%; OR 2.5; 95% CI, 1.1-5.7;  $P = .03$ ) and had a higher mean CES-D score across the intervention period, being 5.6 (SD 5.7) and 4.2 (SD 5.3) at visit 6, respectively, and 5.7 (SD 7.6) and 4.0 (SD 5.0) at visit 12.

## **Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial**

Daly, et al

A phase 2, double-blind, doubly randomized, delayed-start, placebo-controlled study was conducted to assess the efficacy, safety, and dose-response of intranasal esketamine hydrochloride in 67 patients with treatment-resistant depression (TRD). Exclusion criteria included recent or current suicidal ideation with intent to act, suicidal behavior, bipolar or related disorders, psychotic disorder, PTSD, substance/alcohol use disorders in the past year, and recent use of cannabis. In period 1 of the study (days 1-8), participants were randomized (3:1:1:1) to placebo (n = 33), esketamine 28 mg (n = 11), 56 mg (n = 11), or 84 mg (n = 12) twice weekly. In period 2 (days 8-15), 28 placebo-treated participants with moderate-to-severe symptoms were rerandomized (1:1:1:1) to 1 of the 4 treatment arms; those with mild symptoms continued receiving placebo. Participants continued their existing antidepressant treatment during the study. During the optional open-label treatment period (days 15-74), dosing frequency was reduced from twice weekly to weekly, and then to every 2 weeks. The primary efficacy end-point was change from baseline to day 8 (each period) in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. The mean MADRS total score decreased from baseline to day 8 (period 1) and from day 8 to day 15 (period 2) in all groups, with greater improvement in all esketamine dose groups compared with placebo (least squares mean difference ranging from -5.0 to -10.5 in period 1 and from -3.1 to -6.9 in period 2). Change from baseline in the MADRS total score was statistically significantly greater in all 3 esketamine groups than in the placebo group after 1 week of treatment.

## **The Journal of Clinical Psychiatry**

### **JCP Weekly - 1/16/18 - 1/23/18**

## **Validity of the Maudsley Staging Method in Predicting Treatment-Resistant Depression Outcome Using the Netherlands Study of Depression and Anxiety**

Belkum, et al.

The Maudsley Staging Method (MSM) was used to see if it had predictive measure in the degree of treatment-resistant depression outcomes. A total of 643 subjects from the general population, primary care, and secondary care who suffered from current depressive disorder were included from the Netherlands Study of Depression and Anxiety baseline assessment. The primary outcomes were percentage of follow-up time spent in a depressive episode and being “mostly depressed” ( $\geq 50\%$  of the follow-up) between baseline and 2-year follow-up. The MSM predicted “percentage of follow-up time with depression” ( $P < .001$ ) and was associated with being “mostly depressed” (OR = 1.40; 95% CI, 1.23–1.60;  $P < .001$ ). These effects were not modified by having received treatment.

## **Facial Emotion Recognition Performance Differentiates Between Behavioral Variant Frontotemporal Dementia and Major Depressive Disorder**

Chiu, et al.

It is not uncommon for early behavioral variant frontotemporal dementia (bvFTD) and major depressive disorder (MDD) to be misdiagnosed due to their overlapping symptomologies. This prospective cohort study aimed to improve the discrimination between these disorders using a novel facial emotion perception task by rating the intensity of morphed faces on congruent and incongruent basic emotions. The authors compared 25 patients meeting Rascovsky diagnostic criteria for bvFTD, 20 patients meeting DSM-IV criteria for MDD, 21 patients meeting McKhann diagnostic criteria for Alzheimer's disease dementia, and 31 healthy participants. Congruent emotions were underrated in bvFTD patients ( $P < .01$ ), they also overrated incongruent emotions ( $P < .001$ ), resulting in confusion of facial emotions. In contrast, MDD patients overrated congruent negative facial emotions ( $P < .001$ ), but not incongruent facial emotions. In contrast, Alzheimer's disease dementia patients perceived emotions similarly to healthy participants. By using facial emotional recognition, ratings of congruent and incongruent emotions highly discriminated between bvFTD and MDD patients, potentially helping improve the diagnostic certainty in early bvFTD.

## **The Lancet Psychiatry**

### **Volume 5, Issue 2**

#### **Incidence of suicide, hospital-presenting non-fatal self-harm, and community-occurring non-fatal self-harm in adolescents in England (the iceberg model of self-harm): a retrospective study**

Geulayov, et al.

Using multiple sources of data (national mortality, hospital monitoring, school survey), authors estimate the incidence of suicide, hospital-presenting non-fatal self-harm, and community-occurring non-fatal self-harm in adolescents (age 12-17) in England during the years 2011-2013. The incidence of suicide in adolescents aged 12–17 years was 1.5 per 100000 person-years, and the incidences of hospital-presenting and community occurring self-harm were 556 per 100 000 person-years and 5848 per 100000 person-years, respectively. The analyzed data reveals the following rate ratios. For 12-14 years old: For 1 suicide death of a boy, there were 109 who presented to hospital following self-harm, and 3067 who reported self-harm in the community. For 1 suicide death of a girl, there were 1255 hospital-presenting self-harm and 21,995 reported self-harm in the community. For 15-17 years old, the rate ratios were 1: 120: 838 for boys, and 1: 919: 6406 for girls. Hanging or asphyxiation was the most common method of suicide (73%), self-poisoning most common for hospital-presenting self-harm (71%), and self-cutting was the primary method of self-harm used in the community (89%). Findings support an iceberg model of self-harm in which the rate of self-harm in the community (bottom of iceberg) far outweighs the rate of suicide deaths (tip of iceberg), particularly for adolescent girls.

## **Journal of the American Academy of Child and Adolescent Psychiatry**

### **Volume 57, Issue 2**

### **Examining the Association Between Autistic Traits and Atypical Sensory Reactivity: A Twin Study**

Taylor, et al.

This study utilized data from 12,419 Swedish twin pairs ( $n=3,586$  MZ,  $n=8,833$  DZ) to investigate the association between autistic traits and sensory reactivity (SR). Twins ages 9 or 12 (and parents) were evaluated using the A-TAC inventory as well as the ASD module with two validated cutoffs (strict= $\geq 8.5$ , broad= $\geq 4.5$ ). Autistic traits and SR were highly heritable (62-75% and 66-71%, respectively). Phenotypic correlation between autistic traits and SR was moderate and higher in males ( $r_{ph}=.51$  [.49-.52]) than in females ( $r_{ph}=.42$  [.41-.44]). Genetic correlations with SR increased between the broad and strict probands (.72 and .8, respectively). Most phenotypic correlation was explained by genetic factors in males (89%) and females (84%). Phenotypic group correlation between ASD and SR was .57 for the broad proband group, and increased to .64 for the strict proband group. These results indicate utility in SR data incorporation with future attempts at ASD genotyping.

### **Longitudinal Diffusion Tensor Imaging Study of Adolescents and Young Adults With Bipolar Disorder**

Weathers, et al.

In adults with bipolar disorder (BD), neuroimaging has demonstrated decreased structural integrity in the uncinate fasciculus (UF), a white matter tract connecting the amygdala/prefrontal cortex system integral to emotional regulation. This longitudinal study sought to evaluate differences in age- and time-related changes in fractional anisotropy (FA) of the UF in youth with BD. Youth with primary medical/neurological disorders, active/recent substance use, and history of severe concussion were excluded. Two diffusion tensor imaging studies were performed at  $\sim 2.5$  year intervals on youth with BD ( $n=27$ ) and healthy controls (HC) ( $n=37$ ). BD youth were identified via either the SCID (age  $\geq 18$ ) or the K-SADS (age  $< 18$ ). HC youth showed expected and significant UF FA increases with age over time whereas BD youth did not. Of interest, youth with a comorbid diagnosis of BD and ADHD did demonstrate significant increase over time in UF FA relative to BD youth without ADHD ( $p=.02$ ).

### **Biobehavioral Markers of Attention Bias Modification in Temperamental Risk for Anxiety: A Randomized Control Trial**

Liu, et al.

This double-blinded, randomized, control trial sought to examine the effects of a new training protocol for attention bias modification (ABM) on symptomatic, behavioral, and neural risk markers in 9-12 year old children with behavioral inhibition (BI). Using the Behavioral Inhibition Questionnaire, 84 children with BI were identified and assigned to either a 4-session active ABM training ( $n=43$ ) or placebo protocol ( $n=41$ ). Eligible participants also underwent a second visit for fMRI assessment. The C-DISC-IV was utilized before and after all sessions to assess anxiety symptoms. AB threat was measured by a behavioral version of the dot-probe task. Active ABM training showed significant effect on separation anxiety in the ABM vs placebo groups (mean  $-0.05$ , SD 0.58 vs. mean 0.04, SD 0.65), but not social anxiety. ABM did not modify behavioral AB scores. Training effect was significant for clusters within the right insula ( $p=.02$ ) and left ventrolateral prefrontal cortex ( $p=.00$ ). No age effects were observed for all comparisons.

## **Acta Psychiatrica Scandinavica**

### **Volume 137, Issue 1**

#### **Psychotic (delusional) depression and suicidal attempts: a systematic review and meta-analysis**

Gournellis, et al.

This systematic review examined the risk of suicide attempts in unipolar psychotic depression as compared with non-psychotic depression using a meta-analysis of literature found in PubMed, EMBASE, PsycINFO and various databases of the so-called gray literature. Twenty studies were included, encompassing 1,275 patients with psychotic depression and 5,761 non-psychotic depression patients. Despite heterogeneity of the data, this analysis showed that patients with unipolar psychotic depression are at a two-fold higher lifetime (2.11, 95% CI: 1.81-2.47) and acute-phase (1.93, 95% CI: 1.33-2.80) risk of suicide attempts than patients with non-psychotic depression.

#### **Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia**

McCutcheon, et al.

It is often unclear in clinical settings whether inadequate response to antipsychotics in schizophrenia is secondary to medication ineffectiveness or medication under-exposure due to factors such as non-adherence or pharmacokinetics. This study examined the antipsychotic plasma levels in 99 patients provisionally diagnosed with treatment-resistant schizophrenia, not prescribed clozapine, and determines that in this population 35% of plasma levels were subtherapeutic. Of the subtherapeutic levels, 34% were undetectable. Subtherapeutic levels were associated with black ethnicity, lower doses, and subsequent hospital admissions indicating a need to address adherence and/or pharmacokinetic factors as opposed to switching to clozapine in many cases.

#### **Adverse cardiac events in out-patients initiating clozapine treatment: a nationwide register-based study**

Rohde, et al.

Using Danish national registers from 1996-2015 of 3,626 patients who initiated clozapine as an outpatient, this study estimated rates of myocarditis and pericarditis within 2 months of initiation, rates of cardiomyopathy within 1-2 years of initiation, and mortality within 2 months of initiation, as compared to other antipsychotics. The study found that 0.03% developed myocarditis and 0% developed pericarditis within 2 months of clozapine initiation. Within 1 year of initiation, 0.06% of patients developed cardiomyopathy. Within 2 years of initiation, 0.12% of patients developed cardiomyopathy. Rates were similar to other antipsychotics. Pneumonia (23.08%) and stroke (11.54%) were the 2 main causes of death for the 26 patients who died within 2 months of clozapine initiation. Thus, these data indicate that cardiac adverse event from outpatients initiating clozapine are extremely rare and are comparable to the rates observed with other antipsychotics.