Department of Psychiatry

RESEARCH WATCH

March 2018 - Volume 4, Issue 3

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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)
* British Journal of Psychiatry (BJP)
* New England Journal of Medicine (NEJM)

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Highlights

- First placebo-controlled clinical trial of cannabidiol in treatment of schizophrenia shows modest antipsychotic effects of cannabidiol when added to stable antipsychotic regimens. (AJP)
- Data from the Alzheimer's Disease Neuroimaging Initiative shows an associated delay in progression from mild cognitive impairment to dementia in patients with a history of depression treated with long-term SSRIs. (AJP)
- Corticotropin-releasing hormone binding protein gene (CRHBP) may have an important role in modulating SSRI antidepressant treatment response. (AJP)
- British observational study of 9,000 women and their children shows substantial risk for behavioral problems, poor math grades and adolescent depression in the children of women with persistent, severe postpartum depression. (JAMA-P)
- Longitudinal birth cohort study shows large and increasing IQ deficits and slowed developmental growth in neurocognitive functions among individuals with psychotic disorder. (JAMA-P)
- A patient-level mega-analysis shows reduction in HRSD suicidality ratings with SSRI treatment among patients over the age of 24 and no difference relative to placebo in patients under that age. (BJP)
- Dutch RCT suggests that the addition of virtual-reality-based CBT to standard treatment can reduce paranoid ideation and momentary anxiety in patients with a psychotic disorder. (LP)
- 5-year longitudinal study suggests 3 pathways to suicidal behavior in older patients, characterized by i) dementia prodrome, ii) dysfunctional personality traits, and iii) impulsive decision-making and cognitive deficits. (JCP)
- In a large RCT involving military veterans with chronic PTSD, prazosin did not alleviate nightmares or improve sleep quality compared to placebo, contrary to earlier studies. (NEJM)

The American Journal of Psychiatry
Volume 175, Issue 3

Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial
McGuire, et al.

This phase 2, 8-week, multicenter, double-blind, parallel-group study explored the safety and effectiveness of cannabidiol (CBD) as an adjunctive treatment in schizophrenia. Adult patients with schizophrenia were randomized to receive 1000 mg/day of CBD oral solution (N=43) or placebo (N=45) in addition to their current oral antipsychotic medication. Outcomes included assessments of symptom severity, level of functioning, and cognitive performance. At study end, the CBD group had significantly lower levels of positive psychotic symptoms (PANSS difference -1.4 score, 95% CI= -2.5, -0.2), and a significantly higher proportion rated as improved on Clinical Global Impressions (CGI-I) by their clinician (score difference -0.5, 95% CI= -0.8, -0.1) compared to the placebo group. Improvement in cognitive performance and in overall functioning in the CBD group was also greater than placebo group, trending but not reaching statistical significance. Tolerability and rates of adverse events were similar between groups.

Impact of SSRI Therapy on Risk of Conversion From Mild Cognitive Impairment to Alzheimer's Dementia in Individuals With Previous Depression
Bartels, et al.

Authors analyzed data from the multicenter, prospective, longitudinal Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort to examine SSRI treatment in patients with mild cognitive impairment (MCI). ADNI data (including clinical and demographic info, depressive and cognitive variables, ApoE genotyping, and CSF biomarkers) from 755 non-depressed patients were classified into groups of no history of depression, history of depression that went untreated, history of depression treated with SSRI, and history of depression treated with a non-SSRI medication. Data were analyzed using Kaplan-Meier, ANOVA, and covariance with ApoE4 and age as covariates. Results showed that long term treatment with SSRIs (> 4 years) in MCI patients with a history of depression was significantly associated with delayed progression to Alzheimer's dementia by 3 years compared with short term SSRI treatment, non SSRI treatment, or no treatment, and compared with MCI patients with no history of depression. There were no significant differences in CSF biomarkers between groups.

Antidepressant Outcomes Predicted by Genetic Variation in Corticotropin-Releasing Hormone Binding Protein
O'Connell, et al.

A test sample (N=636) from the International Study to Predict Optimized Treatment in Depression

(iSPOT-D) was examined to determine whether variation in five corticotropin-releasing hormone (CRH) and cortisol-related genes contributes to outcomes following acute antidepressant treatment in major depression. Participants were randomly assigned to receive escitalopram, sertraline, or extended-release venlafaxine with clinically indicated dose adjustments made by treating clinicians. Genotyping of 16 HPA axis SNPs within CRH and cortisol related genes was conducted for all participants. Outcome measures included symptom change as indicated by HAM-D, assessed acutely after 8 weeks of treatment. Findings showed that variant rs28365143 in the corticotropin-releasing hormone binding protein gene predicted antidepressant outcomes for remission, response, and symptom change. Those homozygous for the G allele at this SNP had greater rates of remission and response, and symptom reductions, and responded significantly better to SSRIs (escitalopram and sertraline) compared to carriers of A alleles. This genotype was not associated with treatment outcomes for venlafaxine. The effect of genotype on treatment response remained when patients were stratified by race.

Role of Complex Epigenetic Switching in Tumor Necrosis Factor-α Upregulation in the Prefrontal Cortex of Suicide Subjects
Wang, et al.

The underlying mechanisms of critical cytokine gene tumor necrosis factor-alpha (TNF-α) dysregulation in the brain of individuals who died by suicide was studied by examining TNF-α expression in the dorsolateral prefrontal cortex of postmortem brains. TNF-α expression was found to be significantly higher in the dorsolateral prefrontal cortex of individuals who died by suicide, regardless of psychiatric diagnosis, and was also increased in individuals with Major Depressive disorder who died by causes other than suicide. The role of putative microRNAs targeting TNF-α and RNA-binding protein Hu antigen R (HuR) was tested by examining expression of transactivation response RNA binding protein (TRBP). Expression of miR-19a-3p was upregulated specifically in individuals who died by suicide. Despite its ability to directly target TNF-α in vitro, miR-19a-3p showed no interaction with TNF-α in the dorsolateral prefrontal cortex.

JAMA Psychiatry
Volume 75, Issue 3

Association of Persistent and Severe Postnatal Depression With Child Outcomes
Netsi, et al.

This observational study with 9,848 women with varying levels of postnatal depression (PND) and 8,287 children was carried out to examine the association between differing levels of persistence and severity of PND and long-term child outcomes. Depression was defined as persistent when the Edinburgh Postnatal Depression Scale (EPDS) score was above the threshold level at both 2 and 8 months after childbirth. Risk of child behavioral problems at 3.5 years of age was assessed using the Rutter total problems scale, school-leaving mathematics grades at 16 years of age extracted from records of external national public examinations, and offspring depression at 18 years of age using the Clinical Interview

Schedule–Revised. Compared with children of women with PND that did not persist, children of women with severe persistent depression were at increased odds for behavioral disturbances (OR, 4.84; 95% CI, 2.94-7.98), lower mathematics grades at 16 years of age (OR, 2.65; 95% CI, 1.26-5.57), and higher prevalence of depression at 18 years of age (OR, 7.44; 95% CI, 2.89-19.11).

Mortality Rates After the First Diagnosis of Psychotic Disorder in Adolescents and Young Adults
Simon, et al.

A population-based cohort study examined overall and cause-specific mortality during the 3-year period following first diagnosis of a psychotic disorder. A total of 11,713 individuals with first diagnosis of a psychotic disorder were matched to 35,576 outpatient service users and 23,415 members with a first diagnosis of unipolar depression. During the first year, all-cause mortality was 54.6 (95% CI, 41.3-68.0) per 10,000 in the psychotic disorder group compared with 20.5 (95% CI, 14.7-26.3) per 10,000 in the unipolar depression group and 6.7 (95% CI, 4.0-9.4) per 10,000 in the general outpatient group. Deaths due to self-inflicted injury or poisoning were more likely in the new psychotic disorder diagnoses group (HR, 34.93; 95% CI, 8.19-149.10) than in the general outpatient group, but mortality associated with self-harm was not significantly more likely in the psychosis group than in the unipolar depression group (HR, 1.62; 95% CI, 0.92-2.87). Risk of death due to heart disease or diabetes did not differ significantly between the psychotic disorder and the general outpatient groups (HR, 0.78; 95% CI, 0.15-3.96). Between the first and third years after diagnosis, all-cause mortality and injury and poisoning mortality in the psychotic disorder group decreased but remained 3 times as high as in the general outpatient group.

Course of Cognitive Development From Infancy to Early Adulthood in the Psychosis Spectrum
Mollon J, et al.

Data analysis of 4,322 individuals from a longitudinal birth cohort study was carried out to chart the course of general and specific cognitive functions in individuals with psychotic disorders, psychotic experiences, and depression, by comparing them with controls. Individuals with psychotic disorder showed continually increasing deficits between infancy (18 months) and adulthood (20 years) in full-scale IQ (effect size of change [ESΔ] = −1.09, $P = .02$) and nonverbal IQ (ESΔ = −0.94, $P = .008$). The depression group showed a small, increasing deficit in nonverbal IQ (ESΔ = −0.29, $P = .04$) between infancy and adulthood. Between ages 8 and 20 years, the psychotic disorder group exhibited developmental lags in measures of processing speed (ESΔ = −0.68, $P = .001$), working memory (ESΔ = −0.59, $P = .004$), and attention (ESΔ = −0.44, $P = .001$) and large, static deficits in measures of language (ES = −0.87, $P = .005$) and visuospatial ability (ES = −0.90, $P = .001$). There was only weak evidence for cognitive deficits in the psychosis with depression group and the psychotic experiences group.

The Journal of Clinical Psychiatry
Volume 79, Issue 2

Pathways to Late-Life Suicidal Behavior: Cluster Analysis and Predictive Validation of Suicidal Behavior in a Sample of Older Adults With Major Depression
Szanto, et al.

The authors investigated the clinical heterogeneity involved in suicide risk to find predictive pathways to suicidal behavior in older adults. This longitudinal study over 5 years examined distinct associations of clinical and cognitive/decision-making factors with suicidal behavior in 194 older (50+ years) non-demented, depressed patients; 57 non-psychiatric healthy controls provided benchmark data. Three pathways to suicidal behavior in older patients were found, marked by (1) very high levels of cognitive and dispositional risk factors suggesting a dementia prodrome, (2) dysfunctional personality traits, and (3) impulsive decision-making and cognitive deficits. There were significant between-cluster differences in number ($P < .001$) and lethality ($P = .002$) of past suicide attempts and in the likelihood of future suicide attempts ($P = .010$, 30 attempts by 22 patients, 2 fatal) and emergency psychiatric hospitalizations to prevent suicide ($P = .005$, 31 participants).

Inflammation and Improvement of Depression Following Electroconvulsive Therapy in Treatment-Resistant Depression
Kruse, et al.

This study evaluated whether markers of inflammation predicted response to electroconvulsive therapy (ECT) in patients with treatment-resistant depression and to what extent this association differed between men and women. A total of 29 patients with major depressive episode had levels of CRP, IL-6, IL-8, and tumor necrosis factor-α and severity of depressive symptoms (Montgomery-Asberg Depression Rating Scale [MADRS]) prospectively evaluated before ECT treatment, after the second ECT session, and again at the completion of the index treatment series. In multivariate analyses, higher levels of IL-6 at baseline, but not other inflammatory markers or clinical variables, were associated with lower end-of-treatment MADRS score ($P = .01$). When stratified by sex, IL-6 remained a significant predictor of end-of-treatment MADRS for women ($P = .02$) but not men ($P = .1$), and CRP emerged as a significant predictor for women ($P = .04$) but not men ($P = .66$). Assessment of pretreatment inflammatory biomarkers, especially in women, might be useful in guiding treatment decision-making in treatment-resistant depression.

The Lancet Psychiatry
Volume 5, Issue 3

Virtual-reality-based cognitive behavioral therapy versus waiting list control for paranoid ideation and social avoidance in patients with psychotic disorders: a single-blind randomized controlled trial
Pot-Kolder R, et al.

This randomized controlled trial investigated the effects of virtual-reality-based cognitive behavioral therapy (VR-CBT) on paranoid thoughts and social participation. A total of 116 adult patients with a DSM-IV-diagnosed psychotic disorder and paranoid ideation in the past month were randomly assigned to the VR-CBT (n=58) and to the waiting list control group (n=58). VR-CBT consisted of 16 individual therapy sessions (each 1 h long). The primary outcome was social participation, which was operationalized as the amount of time spent with other people, momentary paranoia, perceived social threat, and momentary anxiety. Compared with the control, VR-CBT did not significantly increase the amount of time spend with other people at the post-treatment assessment (3 months from baseline). Momentary paranoid ideation (b= –0·331 [95% CI −0·432 to −0·230], p<0·0001; effect size −1·49) and momentary anxiety (−0·288 [–0·438 to −0·1394]; p=0·0002; −0·75) were significantly reduced in the VR-CBT group compared with the control group at the post-treatment assessment, and were maintained at the follow-up assessment (6 months from baseline).

Journal of the American Academy of Child and Adolescent Psychiatry Volume 57, Issue 3

Effect of Time-Dependent Selective Serotonin Reuptake Inhibitor Antidepressants During Pregnancy on Behavioral, Emotional, and Social Development in Preschool-Aged Children
Lupatelli, et al.

Using prospectively collected data from the Norwegian Mother and Child Cohort Study (MoBa), authors examined the association between prenatal SSRI exposure and child behavioral, emotional, and social development by 5 years of age. At final assessment, the cohort comprised 290 SSRI-exposed and 3,775 nonexposed mothers with self-reported current or previous depression or anxiety. Women taking SSRIs were classified as having early (0–16 weeks), mid (17–28 weeks), or late (≥29 weeks) pregnancy exposure. Child internalizing and externalizing behaviors and temperament were measured at 1.5, 3, and 5 years. Authors found that children exposed to SSRIs in late pregnancy were at increased risk for anxious/depressed behaviors by age 5 years (adjusted β = 0.50; 95% CI = 0.04, 0.96). In absolute terms, the authors concluded that 8 children would be predicted to have anxious/depressed behaviors by 5 years of age for every 100 women exposed to SSRIs in late pregnancy, assuming that 5% of the unexposed experienced the outcome. From among 22 inverse probability of treatment–weighted and inverse probability of censoring–weighted models examining mid and late pregnancy exposure, none of the other time periods or outcomes were statistically significant.

The Effectiveness of School-Based Mental Health Services for Elementary-Aged Children: A Meta-Analysis
Sanchez, et al.

Random-effects meta-analytic procedures were used to synthesize effects of school-based mental health services for elementary school-age children delivered by school personnel and potential

moderators of treatment response. Forty-three controlled trials evaluating 49,941 elementary school-age children met the selection criteria (mean grade 2.86, 60.3% boys). Overall, school-based services demonstrated a small-to-medium effect (Hedges g = 0.39) in decreasing mental health problems, with the largest effects found for targeted intervention (Hedges g = 0.76), followed by selective prevention (Hedges g = 0.67), compared with universal prevention (Hedges g = 0.29). Mental health services integrated into students' academic instruction (Hedges g = 0.59), those targeting externalizing problems (Hedges g = 0.50), those incorporating contingency management (Hedges g = 0.57), and those implemented multiple times per week (Hedges g = 0.50) showed particularly strong effects.

The British Journal of Psychiatry
Volume 212, Issues 2 and 3

Effects of selective serotonin reuptake inhibitors on rating-scale-assessed suicidality in adults with depression
Näslund, et al.

This patient-level mega-analysis of industry-sponsored studies compared the effect of SSRIs on suicidality in adult participants with depression after 6 weeks of treatment relative to placebo. Hamilton Rating Scale for Depression (HRSD) scores were compared among participants taking sertraline, paroxetine, or citalopram (n=5681) and placebo (n=2581). Separate analyses were conducted for young adults (age 18-24; n=537) and adults (age ≥25; n=7725). In the adult cohort, SSRIs reduced the mean rating of the HRSD suicidality item (ES: 0.25 at 6 weeks), risk for aggravation of suicidal ideation (AOR 0.54-0.66; P<0.001), and emergent suicidal behavior (AOR 0.49-0.66, P<0.001). In young adults, SSRI treatment neither reduced nor increased suicidality ratings relative to placebo; however, these results were limited by sample size.

Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis
van Diermen, et al.

Meta-analysis of 2, 193 articles sought to identify reliable predictors of ECT response, with a potential goal of optimizing patient selection and improved response rates. Among 2,193 articles, 34 were included. Presence of psychotic features was found to be a predictor of ECT remission (OR=1.47) and response (OR=1.69). Older age was also a predictor for remission (SMD=0.26) and response (SMD=0.35). Severity of depression did not predict remission, but was significant for response (SMD=0.19). Consideration of data on melancholic symptoms were inconclusive.

The New England Journal of Medicine
Volume 378, Issue 6

Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans
Raskind, et al.

This double-blind, randomized study found that prazosin, an α1-adrenoreceptor antagonist, did not alleviate distressing dreams or improve sleep quality, contrary to results from prior studies. A total of 304 participants from 13 Department of Veterans Affairs medical centers with chronic PTSD reporting frequent nightmares were randomly assigned to prazosin (n=152) and placebo (n=152). Prazosin was administered in escalating divided doses over the course of 5 weeks to a daily maximum of 20 mg in men and 12 mg in women. Outcome measures were tracked from baseline to 10 weeks and 26 weeks on the Clinician-Administered PTSD Scale (CAPS) item B2 "recurrent distressing dreams", Pittsburgh Sleep Quality Index (PSQI) and the Clinical Global Impression of Change (CGIC). At 10 weeks, there were no significant differences between the prazosin group and the placebo group in the mean change from baseline in the CAPS (between-group difference, 0.2; 95% confidence interval [CI], −0.3 to 0.8; P=0.38), in the mean change in PSQI score (between-group difference, 0.1; 95% CI, −0.9 to 1.1; P=0.80), or in the CGIC score (between-group difference, 0; 95% CI, −0.3 to 0.3; P=0.96). There were no significant differences in these measures at 26 weeks or in other secondary outcomes. As discussed by the authors, a possible explanation for these surprising negative results may be selection bias resulting from recruitment of patients who were mainly in clinically stable condition at the time of enrollment.