Department of Psychiatry

RESEARCH WATCH

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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)
* Misc: JAMA

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Highlights

- RCT suggests that lithium and divalproex are similarly well-tolerated in the treatment of acute mania in patients aged 60 years and older, and are similarly effective with lithium showing a greater effect size. (AJP)
- Overall increase in suicide attempts among US adults from 2004-2005 to 2012-2013 has disproportionately affected younger adults with less formal education. (JAMA-P)
- Post-hoc analysis of the CATIE-AD trial shows no significant differences in symptom trajectories between placebo and active drug responders for behavioral and psychological symptoms of dementia. (JCP)
- Taiwanese population study shows a modestly increased seizure risk (OR 1.48) with antidepressant exposure. (JCP)
- Population study of health records shows that when patient differences are accounted for, rates of early medication adherence differ only minimally between individual prescribers. (JCP)
- Danish nationwide cohort study shows that continuation of lithium after an initial diagnosis of end-stage renal disease may be associated with improved renal outcomes than discontinuation. (APS)
- Randomized, sham-controlled study of subcallosal cingulate deep brain stimulation for treatment-resistant depression shows no antidepressant efficacy with the intervention. (LP)
- Meta-analysis shows greater improvement with olanzapine in acute mania in subjects with greater baseline mania severity. (LP)
- International data from WHO surveys suggests that some, but not all, childhood adversities increase the risk of PTSD following traumatic experiences. (BJP)
- RCT reveals no efficacy of sertraline compared to placebo for major depression in non–dialysis-dependent chronic kidney disease. (JAMA)
- Prolonged-release melatonin demonstrated efficacy and safety for the treatment of insomnia in children and adolescents with autism spectrum disorder in an RCT. (JAACAP)
- Data from cohort study suggests that different cannabis use patterns in adolescence and early adulthood have distinctive risk profiles. (JAACAP)

The American Journal of Psychiatry
Volume 174, Issue 11

GERI-BD: A Randomized Double-Blind Controlled Trial of Lithium and Divalproex in the Treatment of Mania in Older Patients with Bipolar Disorder
Young, et al.

This multi-center double-blinded RCT compared acute tolerability and efficacy of lithium and divalproex in treating late-life mania. Adults age 60 years or older with a diagnosis of bipolar I disorder (N=224) and presenting with mania (64.3%), mixed mania (23.2%), or hypomania (12.5%) were randomly assigned to receive target serum concentrations with lithium (N=112) or divaloproex (N=112) over a 9-week period. Primary tolerability outcomes were the sedation item on UKU Side Effect Rating Scale and the proportion of individuals in each group who achieved target serum concentrations. Primary efficacy outcome was change in Young Mania Rating Scale (YMRS) score. A longitudinal mixed model of improvement (change from baseline in YMRS score) significantly favored lithium (difference in scores=3.90). Nine-week response rates did not differ significantly between the lithium and divalproex groups (79% and 73%, respectively). Groups did not differ significantly in rates of sedation or in proportions of patients achieving target serum concentrations.

The 20-Year Longitudinal Trajectories of Social Functioning in Individuals With Psychotic Disorders
Velthorst, et al.

This 20-year prospective study examined differences in trajectories of social functioning across and within a sample of first admission patients with affective and nonaffective psychosis (N=485). Severity of social functioning impairment was assessed by comparing these trajectory groups to a never psychotic match comparison group recruited at the 20-year point (N=262). Data from the Suffolk County Mental Health Project yielded four social functioning trajectory groups across diagnoses: preserved (N=82; 59th percentile of comparison group distribution), moderately impaired (N=148; 17th percentile), severely impaired (N=181; 3rd percentile), and profoundly impaired (N=74; 1st percentile). All groups showed statistically significantly worse social functioning than the comparison group, with the exception of the preserved functioning class. Differences in social functioning among the four groups were evident in childhood. Participants with nonaffective psychosis had more impaired trajectories versus those with affective disorders with schizophrenia spectrum diagnoses overrepresented in the profoundly and severely impaired groups.

JAMA Psychiatry
Volume 74, Issue 11

National Trends in Suicide Attempts Among Adults in the United States
Olfson, et al.

Using data from 69,341 individuals included in the 2004-2005 and 2012-2013 waves of the National Epidemiologic Survey on Alcohol and Related Conditions, this study assesses trends in suicide attempts, adjusting for age, sex and race/ethnicity. Comparison of data from these two periods indicates that overall weighted percentage of adults making a recent suicide attempt increased from 0.62% to 0.79% (ARD, 0.17%; p=0.04). In both studies, approximately 60% of adults with suicide attempts were female. Adjusted risk difference (ARD) was higher for individuals ages 21 to 34 than adult ages 65 and older. Increase in risk was also significantly larger for adults with high school education (0.49%) than among college graduates (0.03%). Antisocial personality disorder, history of violent behavior, and history of anxiety or depressive disorders also increased likelihood of attempting suicide. In both survey groups, nearly two-thirds had a diagnosis of borderline personality disorder.

Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia: A Meta-analysis
Brugger and Howes

This study statistically examines, for the first time, the suspected heterogeneity of regional brain volumes in first-episode schizophrenia, schizoaffective disorder, and schizophreniform disorder. Authors include magnetic resonance imaging (MRI) data from 98 studies of 3,901 patients and 4,040 controls. Comparisons of these images revealed that the variability of the putamen, temporal lobe, thalamus, and third ventricle volumes was greater in first-episode schizophrenia patients, as compared to controls, while indices of heterogeneity were lower for anterior cingulate cortex volumes. The caudate nucleus and frontal lobe showed no variability. The mean volumes of the lateral and third ventricles were greater in first-episode schizophrenia, while the mean volumes of the amygdala, anterior singular cortex, frontal lobe, hippocampus, temporal lobe and thalamus were all lower. Lower variability in the anterior singular cortex, combined with the lower mean volume of this area in individuals with schizophrenia, suggests that changes in this region may be a core disease feature shared across illness subtypes.

Adherence to Depression Treatment in Primary Care: A Randomized Clinical Trial
Sirey, et al.

A randomized control trial was carried out to assess the effectiveness of a psychosocial intervention to improve early adherence among older patients whose primary care physician newly initiated an antidepressant for depression. Participants were 231 adults aged ≥55 years (72% women) without significant cognitive impairment, randomly assigned to the intervention (n = 115) or treatment as usual (n = 116). Participants in the intervention group were 5 times more likely to be adherent (self-reported 80% adherence or greater) at 6 weeks (OR 5.54; P < .001) and 3 times more likely to be adherent at both 6 and 12 weeks (OR 3.27; P < .001). Outcomes at 24 weeks were measured but not reported. Participants from both groups who were 80% adherent at weeks 6 and 12 had a 15% greater improvement in depressive symptoms from baseline over the course of treatment, but was not statistically significant.

Concurrent and Longitudinal Contribution of Exposure to Bullying in Childhood to Mental Health: The Role of Vulnerability and Resilience

Singham, et al.

Analysis of a population-based cohort in England and Wales was done to characterize the contribution of bullying exposure in childhood to multiple mental health domains. Participants were 11,108 twins between 11 and 16 years of age, assessed at 11 and 16 years of age for anxiety, depression, hyperactivity and impulsivity, inattention, conduct problems, and psychotic-like experiences (eg, paranoid thoughts or cognitive disorganization). Phenotypic estimates for the whole sample showed that exposure to bullying in the past year was significantly associated with all mental health outcomes. Monozygotic twin estimates were consistent with a causal influence of childhood exposure to bullying on the total difficulty score, depression, anxiety, conduct problems, child-rated hyperactivity and inattention symptoms. The effects decreased over time. In the monozygotic twins analysis, only paranoid thoughts and cognitive disorganization remained significant at 5 years.

The Journal of Clinical Psychiatry
JCP Weekly - 10/17/17 - 10/24/17

Seizure Risk Associated With Antidepressant Treatment Among Patients With Depressive Disorders
Wu, et al.

This population-based case-crossover study evaluated the risk of seizure associated with antidepressant medication among patients with depressive disorders. A total of 10,002 patients were included from a Taiwanese total population health insurance database. Included patients presented to the emergency department or hospital due to new-onset seizure after receiving antidepressants. The effects of class and dose of antidepressant on seizure risk were explored, using a conditional logistic regression model adjusting for concomitant medications. Antidepressant exposure was positively associated with increased seizure risk (OR = 1.48, 95% CI, 1.33–1.64). Among the antidepressants, the increases in seizure risk of bupropion (OR = 2.23, 95% CI, 1.58–3.16), selective serotonin reuptake inhibitors (OR = 1.76, 95% CI, 1.55–2.00), serotonin and norepinephrine reuptake inhibitors (OR = 1.40, 95% CI, 1.10–1.78), and mirtazapine (OR = 1.38, 95% CI, 1.08–1.77) showed clear dose-response effects. The seizure risk was highest among patients aged between 10 and 24 years and patients with major depression.

Placebo Effects in the Treatment of Noncognitive Symptoms of Alzheimer's Disease: Analysis of the CATIE-AD Data
Ozawa, et al.

This post hoc analysis of data from 371 patients with Alzheimer's disease in Phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness for Alzheimer's disease (CATIE-AD) compared symptom trajectories between placebo and active drug responders, and sought to identify optimal criteria for identification of placebo responders in patients with behavioral and psychological symptoms. Patients were randomly assigned to double-blind treatment with olanzapine, quetiapine,

risperidone, or placebo. Trajectories of change in Brief Psychiatric Rating Scale (BPRS) and Neuropsychiatric Inventory (NPI) scores were compared between placebo and active drug responders. Placebo and active drug responders showed comparable trajectories in symptom improvement throughout the treatment period of 8 weeks and up to week 12. BPRS score reduction at week 2 predicted placebo response at week 8 (OR=1.13; $P < .001$). Finally, a 10% reduction in the BPRS and 5% reduction in NPI at week 2 were the best predictors of eventual placebo response at week 8. The authors suggested there may be utility for the placebo lead-in phase to minimize future trial failures of treatment for noncognitive symptoms of Alzheimer's disease.

Does Patient Adherence to Antidepressant Medication Actually Vary Between Physicians?
Simon, et al.

Data from the Mental Health Research Network (MHRN), a consortium of public-domain research centers associated with five large integrated health systems were reviewed to assess whether adherence to antidepressant medication varied between prescribing physicians to address concerns that a variation can be related to quality of care. A total of 150,318 adults starting antidepressant medication were followed for early adherence, defined as any refill or dispensing of antidepressant medication within 180 days of the index prescription. Patient-level demographic and clinical characteristics potentially associated with adherence were identified from health system records. Overall rates of early antidepressant adherence were 82% for psychiatrists and 74% for primary care physicians. After accounting for sampling variation and case mix differences, the range of adjusted early adherence rates (5th to 95th percentiles) was from 72% to 78% for psychiatrists and from 64% to 69% for primary care physicians. The difference between prescribing physicians was determined to be minimal and not an appropriate measure of individual physician performance. The authors believe efforts to improve adherence should emphasize system-level interventions rather than the performance of individual physicians.

The Lancet Psychiatry
Volume 4, Issue 11

Initial symptom severity of bipolar I disorder and the efficacy of Olanzapine: a meta-analysis of individual participant data from five placebo-controlled studies.
Samara, et al.

This individual participant data meta-analysis of double-blind, randomized controlled trials examined the influence of baseline severity in patients with acute mania on the efficacy of olanzapine. The researchers identified that the interaction between baseline severity and treatment was significant (Beta=0.22, p=0.013). The greater the baseline severity, the greater the magnitude of the differences between olanzapine and the placebo was expected. The mean estimated Young Mania Rating Scale (YMRS; range 0-60) scores were reduced at 3 weeks in both groups, but were greater with olanzapine than placebo by 2.56 points for patients with a baseline score of 20-25 (9.26 for olanzapine vs 6.70 for placebo; effect size

0.35), by 4.74 points for a baseline score of 25-35 (14.25 vs 9.51; 0.58), and by 8.01 points for a baseline score of 35-60 (21.72 vs 13.71; 0.70).

Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomized, sham-controlled trial
Holtzheimer, et al.

This prospective, randomized, sham-controlled was conducted to test the safety and efficacy of Deep Brain Stimulation (DBS) of the subcallosal cingulate white matter for treatment-resistant depression. 90 participants were randomly assigned to active (n=60) or sham (n=30) stimulation. The primary outcome was frequency of response (defined as a 40% or greater reduction in depression severity from baseline) averaged over months 4–6 of the double-blind phase. Both groups showed improvement, but there was no statistically significant difference in response during the double-blind, sham-controlled phase (20% response rate in the stimulation vs 17% patients in the control group). 28 patients experienced 40 serious adverse events; eight of these (in seven patients) were deemed to be related to the study device or surgery. This study confirmed the safety and feasibility of subcallosal cingulate DBS as a treatment for treatment-resistant depression but did not show antidepressant efficacy.

Journal of the American Academy of Child and Adolescent Psychiatry Volume 56, Issue 11

Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children With Autism Spectrum Disorder
Gringras, et al.

This RCT aimed to assess the efficacy and safety of prolonged-release melatonin minitablets (PedPRM) versus placebo for insomnia in children and adolescents with autism spectrum disorder (ASD), with or without ADHD comorbidity, and neurogenetic disorders. 125 children and adolescents (2−17.5 years) whose sleep failed to improve on behavioral intervention alone were randomized and double-blinded to receive PedPRM (2 mg escalated to 5 mg) or placebo for 13 weeks. The primary endpoint was caregivers' Sleep and Nap Diary (SND)-reported total sleep time (TST) after 13 weeks of treatment. Participants slept on average 57.5 minutes longer with PedPRM compared to 9.14 minutes with placebo (adjusted mean treatment difference PedPRM–placebo −32.43 minutes; p = .034). Sleep latency (SL) decreased by 39.6 minutes on average with PedPRM and 12.5 minutes with placebo. The rate of participants attaining clinically meaningful responses in TST and/or SL was significantly higher with PedPRM than with placebo (68.9% versus 39.3% respectively; p = .001) corresponding to a number needed to treat of 3.38. PedPRM was generally safe; somnolence was more commonly reported with PedPRM than placebo.

Predicting Persistent, Limited, and Delayed Problematic Cannabis Use in Early Adulthood: Findings From a Longitudinal Study
Hill, et al.

Data from a prospective 20-year cohort study from 1993 to 2015 (the Great Smoky Mountains Study, n=1,229) was used to identify risk profiles associated with following patterns of cannabis use: nonproblematic use; limited problematic use in late adolescence only; persistent problematic use in late adolescence and early adulthood; and delayed problematic use in early adulthood only. The persistent pattern (6.7%) was characterized by more anxiety disorders compared to the limited pattern (13.3%), which had more childhood family instability. The delayed pattern (3.7%) was characterized by more externalizing disorders, maltreatment, and peer bullying in childhood compared to those in nonproblematic users. It appears, therefore, that problematic cannabis use patterns during early adulthood have distinctive risk profiles.

One-Year Outcome for Responders of Cognitive-Behavioral Therapy for Pediatric Obsessive-Compulsive Disorder
Hojgaard, et al.

This study aimed to estimate durability and age-based response/remission rates of CBT for children and adolescents with OCD one year following acute treatment. Using Nordic Long-term OCD Treatment Study data, 177 youth ages 7-17 were identified with an OCD diagnosis and Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) score of ≥16. OCD-related functional impairment was assessed using the Child Obsessive-Compulsive Impact Scale (COIS-R). All participants received 14 weekly 75-minute sessions of manualized, exposure-based CBT and were allowed up to 4 booster sessions per year thereafter. At one-year follow-up, 78.1% of participants met remission criteria (CY-BOCS ≤10), a 10.5% increase in remission from that immediately following treatment. Average reduction in COIS-R scores was 2.84 and 2.05 or the child- and parent- reported scales, respectively. 15.8% relapsed at either 6- or 12-month assessment. While adolescents showed higher response immediately post-treatment than children, there was no significant difference at follow-up. Only adolescents displayed statistically significant continued improvement during follow-up.

Acta Psychiatrica Scandinavica
Volume 136, Issue 6

Continuation of lithium after a diagnosis of chronic kidney disease
Kessing, et al.

In past studies, long-term use of lithium has been associated with a twofold increased risk of chronic kidney disease (CKD) in patients with bipolar disorder. Using Danish health registry data, authors evaluated risk of end-stage renal disease (ESRD) or death with continuation of lithium or anticonvulsant treatment. Overall, within 10 years after initial diagnosis, patients on lithium (N=754) or anticonvulsants (N=5,004) showed absolute rates of end-stage renal disease (ESRD) of roughly 20%. After adjusting for diabetes and hypertension, poisson regression analyses demonstrates that continued lithium treatment after a first diagnosis of CKD was not associated with increased rates of ESRD, which was defined as

requiring dialysis or transplantation. In fact, continuation of lithium was associated with decreased rates of ESRD or death (HR, 0.50); continuing or adding anticonvulsants did not affect the risk. In the subset of patients with bipolar disorder, continuation of lithium was associated with decreased rates of end-stage CKD, while continuation of other anticonvulsants was not. Limitations of this study include a paucity of detailed data on severity of renal disease, treatment adherence, comorbid psychiatric and medical conditions, and details of ongoing clinical management.

Melatonin as a treatment for mood disorders: a systematic review
De Crescenzo, et al.

A systematic review examined evidence for efficacy and acceptability of melatonin in comparison to placebo in treating symptoms of major depression, bipolar disorder, and seasonal affective disorder. A comprehensive literature search identified eight RCTs (total N=289), which used melatonin as augmentation to treat bipolar disorder (1 study), unipolar depression (3 studies), and seasonal affective disorder (4 studies). Primary outcomes were mean change in HDRS, MADRS, or QIDS-C16, and/or YMRS after 4 weeks of treatment. Secondary outcomes included acceptability and tolerability. Studies used various methodologies and found inconsistent results pertaining to melatonin efficacy for mood. All trials showed good tolerability and acceptability of melatonin versus placebo. A quantitative data analysis of 3 studies compared melatonin as add-on to standard therapy versus placebo in unipolar depression and seasonal affective disorder. Results showed a modest improvement in mood with patients treated with melatonin augmentation, but this did not reach significance (SMD= 0.37; *p*=0.09).

British Journal of Psychiatry
Volume 211, Issue 5

Childhood adversities and post-traumatic stress disorder: evidence for stress sensitisation in the World Mental Health Surveys
McLaughlin, et al.

This study sought to examine the association of particular types of childhood adversities with increased risk of PTSD after exposure to trauma. Respondents (N=27,017) from 18 countries were identified using data from the WHO World Mental Health Surveys. Childhood adversities included interpersonal loss, parental maladjustment, maltreatment, physical illness, and economic adversity. Traumatic events included exposure/participation in organized violence, physical violence victimization, sexual violence, and accidents/injuries. Mental disorders were assessed using the Composite International Diagnostic Interview. Four childhood adversities (physical and sexual abuse, neglect, parent psychopathology) were associated with similarly increased odds of PTSD following traumatic experiences (OR=1.8), whereas the other eight childhood adversities (such as parent death, parent divorce, parent substance misuse) assessed did not predict PTSD. Childhood adversity–PTSD associations did not vary across traumatic experience types, but were stronger in childhood-adolescence and early-middle adulthood than later

adulthood. Limitations of this study include retrospective reports, recall bias, and structured diagnostic interview rather than clinician-administered interview.

Miscellaneous

JAMA

Effect of Sertraline on Depressive Symptoms in Patients With Chronic Kidney Disease Without Dialysis Dependence: The CAST Randomized Clinical Trial

Hedayati, et al.

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A randomized placebo-controlled trial was carried out to evaluate whether treatment with sertraline improves depressive symptoms in patients with non–dialysis-dependent chronic kidney disease and major depressive disorder. Participants were randomized to sertraline (n = 102) for 12 weeks at an initial dose of 50 mg/d (escalated to a maximum dose of 200 mg/d based on tolerability and response) or matching placebo (n = 99). The primary outcome was improvement in depressive symptom severity from baseline to 12 weeks determined by the QIDS-C16 (score range, 0-27; minimal clinically important difference, 2 points). The QIDS-C16 score changed by −4.1 in the sertraline group and by −4.2 in the placebo group. There was no significant difference in change in score in the sertraline group compared to placebo group. Secondary outcomes included improvement in quality of life (Kidney Disease Quality of Life Survey–Short Form), showing no difference between groups. Reported side effects, nausea or vomiting, and diarrhea occurred more frequently in the sertraline group compared to placebo (22.7% vs 10.4%, respectively for nausea or vomiting; and 13.4% vs 3.1%, respectively for diarrhea).