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Research Watch is an initiative by the residents of University Hospitals Cleveland Medical Center/ Case Western Reserve University; it aims to inform psychiatry residents and faculty of notable articles published in prominent research journals.

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: Medscape, Retraction Watch, BMJ

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Highlights

- Epidemiological data suggests decline in substance-use related events during treatment with stimulants or atomoxetine in adolescent and adult patients with ADHD. (AJP)
- RCT suggests tramadol ER is more effective than clonidine and comparable to buprenorphine in reducing opioid withdrawal symptoms during a residential tapering program. (JAMA-P)
- Randomized study shows that a transdiagnostic CBT protocol produces outcomes equivalent to disorder-specific CBT protocols for panic disorder, GAD, social anxiety disorder, and OCD. (JAMA-P)
- Continued lisdexamfetamine treatment is associated with lower relapse risk for binge eating disorder over 6 months than placebo. (JAMA-P)
- Functioning impairments following remission of anxiety disorder appear to be continuations of premorbid lower functioning. (JCP)
- Open-label Japanese study shows that preventive effect of lamotrigine on manic relapse in bipolar II is better than in bipolar I disorder. (JCP)
- Population cohort study shows that in the elderly, depressive symptom severity is negatively associated with bone mineral density. (JCP)
- Retrospective cohort study of discordant twins shows frequent cannabis use associated with major depression and suicidal ideation. (LP)
- Meta-analysis suggests that haloperidol may have inferior efficacy to SGAs in the treatment of first-episode schizophrenia. (LP)
- RCT demonstrates efficacy of aripiprazole compared to placebo for the maintenance treatment of adolescent schizophrenia. (JAACAP)
- Substance use disorders and conduct disorder – but not ODD – are more likely to emerge in adolescents with prior trauma. (JAACAP)
- FDA has approved phase 3 clinical trials of MDMA-assisted psychotherapy for treatment of PTSD. (Medscape)
- A meta-analysis of 28 relapse prevention trials in patients with remitted anxiety disorders shows clear benefit of continuing treatment up to one year for both relapse rate and time to relapse. (BMJ)

The American Journal of Psychiatry

Volume 174, Issue 9

Stability of and Factors Related to Medical Student Specialty Choice of Psychiatry

Goldenberg, et al.

Authors used AAMC survey data to examine the medical student choice of psychiatry as a career as compared to other specialties. Data from 2013 and 2014 were obtained from the AAMC Medical School Graduation Questionnaire (GQ) completed at the end of medical school (n=29,713), which was matched on an individual basis to previous responses on the Matriculating Student Questionnaire (MSQ) completed at the beginning of medical school. Psychiatry specialty choice increased from 1.6% at matriculation to 4.1% at graduation. Of those who chose psychiatry at matriculation, 50.2% maintained this decision to graduation, a higher rate than any other specialty. However, almost 80% of future psychiatrists did not indicate an inclination toward the specialty at matriculation. Factors most highly associated with psychiatry specialty choice included an excellent rating on psychiatry clerkship (OR= 2.66), undergrad psychology major (OR= 2.58), and value placed on work-life balance (OR= 2.25).

ADHD Medication and Substance-Related Problems

Quinn, et al.

This observational study used within-individual comparisons from a large U.S sample to examine the concurrent and long-term associations between pharmacological ADHD treatment and substance-related events (i.e., ED visits related to substance use disorders). Commercial health care claims from 2,993,887 adolescent and adult patients diagnosed with ADHD were analyzed. Risk of substance-related events was compared during months in which patients received prescribed stimulants or atomoxetine relative to months during which they were not. Male patients had a 35% decline (OR= 0.65, 95% CI= 0.64-0.67) in events when receiving ADHD medication, and females had 31% lower odds of concurrent substance-related events (OR=0.69, 95% CI= 0.67-0.71). Substance use-related events similarly declined for a period of 2 years after treatment with ADHD medication in males (19% reduction) and females (14% reduction). There was no evidence for increased risk of problems related to substance use, and findings were similar when conducted for stimulant treatments alone.

A Brain Model of Disturbed Self-Appraisal in Depression

Davey, et al.

This case-control study examined the role of the medial prefrontal cortex in the disturbed self-appraisal processes implicated in depression. Authors applied a dynamic network model of self-directed cognition to functional MRI data from 71 unmedicated adolescents and young adults with moderate to severe depression and compared with 88 matched healthy controls. Dynamic causal models were developed for comparison between groups. Results demonstrated an exaggerated regulatory effect of the medial prefrontal cortex (MPFC) on the posterior cingulate cortex (PCC), with self-appraisal causing more

negative modulation between the two in the depressed versus the control group (OR=0.54, 95% CI= 0.38, 0.77). Modulation strength of MPFC and PCC connectivity was inversely related to behavioral characteristics of concentration difficulties and inner tension ($r=-0.32$; 95% CI= -0.51, -0.08; $p=0.01$).

JAMA Psychiatry

Volume 74, Issue 9

Efficacy of Tramadol Extended-Release for Opioid Withdrawal: A Randomized Clinical Trial

Dunn, et al.

A randomized clinical trial compared tramadol extended-release (ER), clonidine, and buprenorphine in the treatment of supervised opioid withdrawal. Among 103 participants meeting *DSM-IV* criteria for opioid dependence, opioid withdrawal suppression was monitored using the Clinical Opiate Withdrawal Scale (COWS) score and the Subjective Opiate Withdrawal Scale (SOWS) score during and after a taper. Following morphine stabilization, participants were randomized (1:1:1) to a 7-day taper using clonidine ($n=36$), tramadol ER ($n=36$), or buprenorphine ($n=31$) then crossed-over to 7 day placebo treatment. Buprenorphine participants (28 [90.3%]) were significantly more likely to be retained at the end of taper than clonidine participants (22 [61.1%]); tramadol ER participants did not differ significantly from either group (26 [72.2%]). Clonidine participants experienced significantly more severe withdrawal symptoms compared with tramadol ER ($P=.02$) and buprenorphine ($P<.001$) participants during the taper but not post-taper phases. Difference between tramadol ER and buprenorphine was not significant.

Effect of Buprenorphine Weekly Depot (CAM2038) and Hydromorphone Blockade in Individuals With Opioid Use Disorder: A Randomized Clinical Trial

Walsh, et al.

This 3-week inpatient, randomized, double-blind, within-patient phase 2 trial examined the ability of novel once-weekly subcutaneous buprenorphine depot formulation, CAM2038, in producing opioid blockade and opioid withdrawal suppression. CAM2038 was administered at 2 doses, 24 mg and 32 mg, 46 healthy, non-treatment-seeking volunteers with moderate-to-severe opioid use disorder. Subjective drug-liking response after IM injection of hydromorphone was measured with a visual analog scale. Both doses were safely tolerated and produced immediate and sustained opioid blockade and withdrawal suppression. The results support the use of this depot formulation for treatment initiation and stabilization of patients with OUD, with the further benefit of obviating the risk for misuse and diversion of daily buprenorphine while retaining its therapeutic benefits.

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders Compared With Diagnosis-Specific Protocols for Anxiety Disorders: A Randomized Clinical Trial

Barlow, et al.

In this randomized clinical equivalence study, 223 patients with principal diagnoses of panic disorder

with or without agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, or social anxiety disorder were randomly assigned to receive 16 sessions of the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP), to receive 16 to 21 weeks of a Single-Disorder Protocol (SDP), or to a waitlist control. Patients were more likely to complete the UP than the SDPs (odds ratio 3.11). Measures of clinical severity at baseline, after treatment, and at 6-month follow-up showed superiority of UP and SDPs to the waitlist control, as well as statistical equivalence between the UP and SDPs, suggesting that it may be possible to use one protocol instead of multiple to treat commonly occurring anxiety and depressive disorders.

Efficacy of Lisdexamfetamine in Adults With Moderate to Severe Binge-Eating Disorder: a Randomized Clinical Trial

Hudson, et al.

A randomized withdrawal study of lisdexamfetamine (Vyvanse) was conducted at 49 clinical research sites. Participants (n=418) met *DSM-IV-R* binge-eating disorder criteria and had ≥ 3 binge-eating days/week for 14 days before open-label baseline and Clinical Global Impressions-Severity scores indicating moderate severity at screening and open-label baseline. Following a 12-week open-label phase, responders were randomized to placebo or continued lisdexamfetamine for a 26-week double-blind withdrawal phase. Lisdexamfetamine was superior to placebo for time to relapse, with 3.7% of the lisdexamfetamine group and 32.1% of the placebo group meeting relapse criteria.

Risk of Suicide Attempt Among Soldiers in Army Units With a History of Suicide Attempts

Ursano, et al.

This longitudinal cohort study evaluated the administrative records of 9650 active-duty, enlisted soldiers who were medically documented to have attempted suicide from 2004 through 2009, and 153,528 control person-months. Regression analysis examined past-year suicide attempts in the soldier's unit as a predictor of subsequent suicide attempt, controlling for sociodemographic features, service-related characteristics, prior mental health diagnoses, and other unit variables (including suicide-, combat-, and unintentional injury-related unit deaths), as well as the influence of military occupational specialty (MOS) and unit size. Soldiers were found to be more likely to attempt suicide if their unit had experienced ≥ 1 suicide attempt(s) in the past year, with the odds increasing as the number of attempts increased. This factor was significant regardless of the soldiers' MOS or unit size.

The Journal of Clinical Psychiatry

JCP Weekly 8/15/17 - 8/22/17

Limited Functioning After Remission of an Anxiety Disorder as a Trait Effect Versus a Scar Effect: Results of a Longitudinal General Population Study

Schopman, et al.

This population study from the Netherlands Mental Health Survey and Incidence Study-2 assessed the remission state after an anxiety disorder. The authors examined whether impairments in mental and physical functioning following remission were a continuation of premorbid lower functioning (trait effect), due to impairments that develop during the anxiety disorder and persist beyond recovery (scar effect), or both. When compared against healthy controls, those with anxiety disorders showed significant impairment in mental functioning ($P < 0.001$) and physical functioning ($P < 0.001$) prior to the onset of anxiety disorders, a trait effect. No scar effect was found with exception to a subgroup with recurrent anxiety disorders ($P = 0.03$). Relapse prevention may help prevent mental scarring.

Preventive Effects of Lamotrigine in Bipolar II Versus Bipolar I Disorder

Terao, et al.

There has been a limited amount of research on mood stabilizers preventive effects in Bipolar II disorder. This study explored the preventive effects of Lamotrigine in Japanese patients with Bipolar I (BP1) versus Bipolar II (BP2) over a 1-year period. Lamotrigine significantly prolonged the time to recurrence/relapse of mania-related episodes in BP2 patients compared with BP1 patients ($P = .0110$). However, there was no difference between the bipolar patient groups in the time to major depressive episodes ($P = .2468$), indicating that the preventive effect of lamotrigine on recurrence/relapse of major depressive episodes in BP2 patients is similar to that in BP1 patients. The estimated times to recurrence/relapse of mood episodes by bipolar diagnosis (25th percentile) were 71 days and 183 days for BP1 and BP2, respectively. This study suggests that lamotrigine may have greater mania-related mood stabilization efficacy in maintenance treatment of BP2 compared to BP1.

Association Between Bone Mineral Density and Depressive Symptoms in a Population-Based Sample

Hlis, et al.

This population-based cohort study assessed the relationship between bone mineral density (BMD) and depressive symptoms. The authors used data from the second phase of the Dallas Heart Study (DHS-2), a large multiethnic population sample in Dallas County. The 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR16) was used to measure depressive symptoms. QIDS-SR16 score did not significantly predict BMD in the overall DHS-2 sample, however, in those aged 60 years or older ($n = 465$), QIDS-SR16 score was a significant negative predictor of BMD at the lumbar spine and total hip ($\beta = -0.14$, $P = .003$ and $\beta = -0.12$, $P = .006$, respectively). Results suggest that diagnosis and treatment of depressive symptoms may be of clinical importance in older individuals, a subgroup at high risk for osteoporosis and fractures.

The Lancet Psychiatry

Volume 4, Issue 9

Major depressive disorder, suicidal thoughts and behaviors, and cannabis involvement in discordant twins: a retrospective cohort study

Agrawal, et al

This logistic regression analysis aimed to identify the associations between aspects of cannabis use, MDD, and suicidal thoughts and behaviors and examine whether such association persist after accounting for those predisposing factors, including genetic liability and early family environment, that are shared by identical twins who are discordant for cannabis exposure. The researchers did the analysis of cannabis use from retrospective data on same-sex male and female twin pairs drawn from 3 studies that had recruited twins from the Australian Twin Registry. Prevalence of MDD ranged from 20.3% to 28.3%. The monozygotic twin who used cannabis frequently (>100 times) was more likely to report MDD (odds ratio 1.98, 95% CI 1.11-3.53) and suicidal ideation (2.47, 1.19-5.10) compared with their identical twin who had used cannabis less frequently, even after adjustments for covariates.

Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses

Zhu, et al.

Authors conducted a systematic review with pairwise and network meta-analyses of efficacy and tolerability of antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia. For overall reduction of symptoms, amisulpride (SMD -0.37, 95% CI -0.61 to -0.14), olanzapine (-0.25, -0.48 to -0.01), and risperidone (-0.14, -0.27 to -0.01) were significantly more efficacious than haloperidol, but the evidence was very low to moderate quality. Olanzapine was superior to haloperidol and risperidone for reduction of negative symptoms. (There was not enough data for aripiprazole to be included in the efficacy comparisons). Several second-generation antipsychotics were superior to haloperidol in terms of all-cause discontinuation. Quetiapine was associated with less akathisia than haloperidol, aripiprazole, risperidone, and olanzapine, but again, evidence was very low to low quality. Authors conclude that haloperidol seems to be a suboptimum treatment option for acute treatment of first-episode schizophrenia, with little differences between second-generation antipsychotics.

Journal of the American Academy of Child and Adolescent Psychiatry

Volume 56, Issue 9

Trauma Exposure and Externalizing Disorders in Adolescents: Results From the National Comorbidity Survey Adolescent Supplement

Carliner, et al.

This study examined the association of potentially traumatic events (PTEs) with externalizing disorders (EDs) using data from youths aged 13-18 (N=6,379) who participated in the National Comorbidity Survey Replication - Adolescent Supplement. The Composite International Diagnostic Interview for DSM-IV was used to assess PTEs and EDs. Youth self-report only was used for substance use disorders (SUD). Analyses were controlled for parental psychopathology and substance misuse as well as ADHD among

adolescents. All PTEs were associated with higher risk for SUD but not ODD. Interpersonal violence in females was associated with higher risk for conduct disorder (CD). ODD and CD were associated with higher risk for later PTEs. SUD was associated with lower risk for exposure to PTEs, potentially explained by higher mean age of onset of SUD vs. PTEs.

Oral Aripiprazole as Maintenance Treatment in Adolescent Schizophrenia: Results From a 52-Week, Randomized, Placebo-Controlled Withdrawal Study

Correll, et al.

This double-blind, placebo-controlled randomized withdrawal design study evaluated the efficacy, safety, and tolerability of aripiprazole in adolescents with schizophrenia. Adolescents were first cross-titrated to and stabilized on oral aripiprazole. In a double-blind maintenance phase, participants were randomized to aripiprazole (N=98) or placebo (N=48). The trial was terminated early on data monitoring committee recommendation that it be terminated after the 37th impending relapse event, therefore only 21 participants completed the entire 52 weeks of the study. Treatment with aripiprazole was associated with a significantly longer time to exacerbation of psychotic symptoms/impending relapse compared with placebo (hazard ratio=0.46, 95% CI = 0.24–0.88). 19.4% of aripiprazole subjects met criteria for psychosis exacerbation/impending relapse compared to 37.5% with placebo. Mean daily dose of aripiprazole was 19.2 mg. Higher dose aripiprazole (20-30mg) was associated with longer time to exacerbation and lower relapse rate vs. placebo (25.0% vs. 54.6%). Treatment-emergent adverse events, including EPS, weight gain and somnolence, were similar between the two groups or lower with aripiprazole.

National Trends in Substance Use and Use Disorders Among Youth

Han, et al.

The objective of this study was to assess 12-month prevalence and trends of substance use and SUDs among 288,300 US youth ages 12-17 using data from the National Surveys on Drug Use and Health. The survey excluded youth who were homeless, active military, or incarcerated. Between 2002 and 2014, prevalence of any substance use and SUDs decreased by 27.1% and 28.9%, respectively, while mean age of first use increased. However, increased prevalence was found of marijuana and alcohol use only (55.0%) and marijuana use only (128.6%) and multiple substance use was associated with SUDs. Increased age of first use was associated with decreased any substance use and increased age, parental disapproval of cigarettes, and seatbelt-wearing were associated with a decrease in SUDs.

Prevalence and Correlates of Suicidal Ideation Among Transgender Youth in California: Finding From a Representative, Population-Based Sample of High School Students

Perez-Brumer, et al.

This study assessed past-year SI and related psychosocial factors among transgender youth grades 9-12. Data were derived from the full California Healthy Kids Survey (N=576,380) and the representative Biennial Statewide California Student Survey (N=25,493). Of transgender youth (N=7,653, mean

age=15.29), 49.49% identified as heterosexual. Prevalence of SI was 33.73% for transgender vs. 18.85% for non-transgender youth. AOR for SI in transgender youth of the representative sample was 2.99. Higher odds of SI were noted with depressive symptoms (AOR 5.44) and school-based victimization (AOR: 1.72). Depression attenuated the association between gender identity and suicidal ideation by 17.95% and victimization by 14.71%. Identifying as LGB was associated with SI in the full sample.

Miscellaneous

Medscape: FDA Okays Clinical Trial Testing of Psychedelic Drug for PTSD

<http://www.medscape.com/viewarticle/885042>

“The US Food and Drug Administration (FDA) has granted breakthrough therapy designation to MDMA (3,4-methylenedioxymethamphetamine) as an adjunct to psychotherapy for adults with posttraumatic stress disorder (PTSD).

According to the Multidisciplinary Association for Psychedelic Studies (MAPS), the FDA has agreed on the design of two upcoming phase 3 trials of the drug, also known as ecstasy, in patients with severe PTSD.

Completed phase 2 trials from MAPS included 107 patients with treatment-resistant PTSD (mean duration, 17.8 years). Combined results showed that after three sessions of MDMA-assisted psychotherapy, 61% of the participants no longer met PTSD criteria 2 months post treatment. This number increased to 68% 1 year post treatment. Full data from these trials are expected to be published soon.”

Retraction Watch: Ketamine-depression paper retracted following investigation at Yale

<http://retractionwatch.com/2017/08/28/ketamine-depression-paper-retracted-following-investigation-yale/>

Retraction Watch reports that *International Journal of Neuropsychopharmacology* has retracted a 2011 paper investigating the use of rapid intravenous injection of ketamine to treat patients with severe depression following an investigation at Yale University. [Larkin GL, Beautrais, AL (2011). A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *Int J Neuropsychopharmacol* 14: 1127–1131.]

Yale University conducted an investigation that determined that the description of the research was not accurate. The article misrepresented both the protocol-specified doses and the actual delivered doses of ketamine. Further details of the investigation have not been released. The study found that all “14 patients attained remission within 1 week of the treatment, and most met response criteria 10 days after treatment” with minimal side effects. It is pertinent to note that other investigators have failed to replicate the results of rapid IV injection of ketamine (over 1-2 min); it has been poorly tolerated and not

found more effective than other ways of administering ketamine.

The BMJ

Volume 358

Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials

Batelaan, et al.

<https://doi.org/10.1136/bmj.j3927>

Systematic review and meta-analysis of relapse prevention trials examined risk of relapse and time to relapse after discontinuation of antidepressants in patients with anxiety disorders, as well as relationships between relapse risk and type of anxiety disorder, type of antidepressant, mode of discontinuation, duration of treatment and follow-up, comorbidity, and allowance of psychotherapy. Meta-analysis included 28 randomized controlled trials of patients (n=5230) with anxiety disorders who responded to antidepressants, were then continued on therapy or switched to placebo, and followed for up to one year. Discontinuation of antidepressants increased odds of relapse compared to continuation of antidepressants (summary odds ratio 3.11, 95% CI 2.48-3.89). Subgroup analyses and meta-regression showed no statistical significance. At up to one year of follow-up, time to relapse was shorter with treatment discontinuation (summary hazard ratio 3.63, 2.58 to 5.10, n=11 studies). Summary relapse prevalences were 36.4% (30.8% to 42.1%; n=28 studies) for the placebo group and 16.4% (12.6% to 20.1%; n=28 studies) for the antidepressant group, but prevalence varied across studies.