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)
* British Journal of Psychiatry (BJP)
* Acta Psychiatrica Scandinavica (APS)

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Highlights

- A 20-year follow-up study using a Finnish nationwide database indicates that antipsychotics substantially decrease, not increase, the risk of death after first episode schizophrenia and decreases risk of relapse. (AJP)
- An RCT shows equivalent clinically significant reductions of borderline symptoms with placebo and lamotrigine, with a large effect size. (AJP)
- A systematic review and meta-analysis suggests that exposure to hypertensive disorders of pregnancy is associated with a small but significant increase in the odds of autism spectrum disorder and ADHD. (JAMA-P)
- An RCT shows that dialectical behavior therapy significantly reduces self-harm in adolescents over a 6-month treatment period. (JAMA-P)
- A systematic review and meta-analysis indicates that the prevalence of MDD is higher among individuals with vascular dementia compared to Alzheimer's disease. (JCP)
- In a placebo-controlled trial involving patients with major depressive disorder and mixed features, lurasidone was not associated with sexual dysfunction. (JCP)
- A large randomized controlled trial shows that an automated psychological intervention delivered by immersive VR is highly effective for reduction of fear of heights. (LP)
- A systematic review and meta-analysis finds no evidence of increased mortality related to acute antipsychotic drug effects; however, an increased mortality risk in people with dementia was observed in secondary analyses. (LP)
- A longitudinal cohort study indicates that childhood interpersonal callousness and childhood anxiety predict increased and decreased adult criminal offending, respectively. (JAACAP)

The American Journal of Psychiatry
Volume 175, Issue 8

The Clinical Effectiveness and Cost-Effectiveness of Lamotrigine in Borderline Personality Disorder: A Randomized Placebo-Controlled Trial
Crawford, et al.

A multicenter, double-blind, placebo-controlled randomized trial evaluated the clinical efficacy and cost-effectiveness of lamotrigine for treatment of borderline personality disorder. The authors recruited 276 adults meeting criteria for borderline personality disorder without comorbid bipolar affective disorder or psychosis, extant mood stabilizer use or pregnancy risk. These individuals were randomly assigned to receive placebo or up to 400 mg/day lamotrigine. The primary outcome measure was score on the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) at 52 weeks. A total of 195 patients were evaluated at 52 weeks, at which point 49 (42%) individuals in the lamotrigine group and 58 (42%) were taking study medication. Mean ZAN-BPD score was 11.3 (SD=6.6) and 11.5 (SD=7.7) in the lamotrigine and placebo groups, respectively. No evidence of differences in secondary outcomes, including depressive symptoms, deliberate self-harm, social function, health-related quality of life, resource use and costs, side effects, and adverse events was apparent. The total yearly cost per participant in the study was $17,785 in the lamotrigine arm and $12,340 in the placebo arm.

Familiality of Psychiatric Disorders and Risk of Postpartum Psychiatric Episodes: A Population-Based Cohort Study
Bauer, et al.

Linked data from Danish birth and psychiatric registries was evaluated for familial risk of postpartum psychiatric episodes in a national population-based cohort. Probands were first-time mothers who were born in Denmark after 1970 and who gave birth after age 15 (N=362,462). Primary exposure was a diagnosed psychiatry disorder in a relative. Cox regression models were used to estimate the hazard ratio of postpartum psychiatric disorders. Overall, the relative risk of psychiatric disorders in the postpartum period was elevated when first-degree family member carried a diagnosis of a psychiatric disorder (hazard ratio=1.45, 95% CI=1.28-1.65) and was highest when proband mothers had a first-degree relative with bipolar disorder (HR=2.86, 95%CI=1.88-4.35). There were no differences by gender of the family member, and associations were stronger among mothers without mental health histories.

20-Year Nationwide Follow-Up Study on Discontinuation of Antipsychotic Treatment in First-Episode Schizophrenia
Tiihonen, et al.

The authors utilized nationwide databases to investigate the use of antipsychotic prophylaxis following the first 5 years of illness. Additionally, they explored the effect of antipsychotics on mortality in patients with schizophrenia in patients followed since their first episode. Antipsychotic-naïve individuals

were identified from a Finnish database of over 23,000 patients who had an initial hospitalization for schizophrenia between 1996-2014. These 8,700 first-episode patients were followed for a maximum of 20 years with hospital admissions identified through the nationwide medication registry. Findings suggested that risk of hospitalization increased after discontinuation of antipsychotics, but also that the risk of relapse increased in proportion to duration of prior treatment. The lowest risk of rehospitalization was observed for patients using antipsychotics continuously followed by those who discontinued therapy immediately following discharge from their first inpatient hospitalization (HR=1.63, 95% CI=1.57-1.75). Risk increased sevenfold when the period of prior treatment had been 5 years or longer. Among nonusers of medication (N=4,217), risk of death was more than 200% higher than in those who continued taking antipsychotics from their first hospitalization (N=3,217). In patients who discontinued antipsychotics within 1 year, the death rate was 174% higher.

Prevalence and Correlates of Prescription Stimulant Use, Misuse, Use Disorders, and Motivations for Misuse Among Adults in the United States
Compton, et al.

A nationally representative household population study of adults age 18 or older from the 2015 and 2016 National Surveys on Drug Use and Health (N=102,000) measured prescription stimulant use, use without misuse, misuse without disorder, and misuse with use disorder. Among American adults, 6.6% used prescription stimulants. Of these, 4.5% used without misuse, 1.9% misused without use disorders, and 0.2% had use disorders. Individuals with past-year prescription stimulant use disorders did not differ from those with misuse without disorders in any of the sociodemographic characteristics. The most common motivation for misuse was cognitive enhancement (56.3%). The most common source of misused prescriptions was obtaining free medication from friends or relatives (56.9%) However, more frequent prescription stimulant misuse and use disorders were associated with increased likelihood of obtaining medications from physicians or from drug dealers or strangers.

JAMA Psychiatry
Volume 75, Issue 8

Efficacy of Dialectical Behavior Therapy for Adolescents at High Risk for Suicide: A Randomized Clinical Trial
McCauley, et al.

This randomized clinical trial compared dialectical behavior therapy (DBT) with individual and group supportive therapy (IGST) for reducing suicide attempts, non-suicidal self-injury, and overall self-harm among youth ages 12 to 18 years of age with at least one prior suicide attempt, elevated prior-month suicidal ideation, lifetime self-injury repetition of at least three episodes with at least one episode occurring in the 12 weeks before screening, and at least 3 borderline personality disorder criteria. At four academic medical centers, a total of 173 participants (94.8% female, 56.4% white, mean age 14.89 years) were randomized between DBT and IGST. Results showed that 90.3% of participants receiving

DBT had no suicide attempts in the first 6 months after beginning treatment, versus 78.9% for the IGST group. Similar outcomes were seen when assessing for non-suicidal self-injury. Overall, 47% of the DBT group and 28% of the control group were totally free of self-harm, with a number needed to treat of 6 patients. However, the advantage of DBT decreased over time, with no significant difference between the groups from 6-12 months after beginning treatment.

Examining the Association of Antidepressant Prescriptions With First Abortion and First Childbirth
Steinberg, et al.

This cohort study of 396,397 women born in Denmark from 1980 through 1994 compared the rates of first-time antidepressant prescription redemptions, used as an indication of depression or anxiety, between women who had a first-trimester abortion, women who had a childbirth, and women who did not have a childbirth. Within this population, women who had a first abortion had a higher risk of first-time antidepressant use; however, the fully-adjusted incidence rate ratios (IRRs) between these populations were not statistically significant in the year before the abortion or the year after the abortion and decreased as time from the abortion increased. The fully-adjusted IRRs comparing women who gave birth with women who did not give birth were lower in the year before childbirth but progressively increased for the women giving birth as time after childbirth increased. The strongest risk factors associated with antidepressant use across all cohorts of women were previous psychiatric contact, previous anti-anxiety medication use, and previous anti-psychotic medication use.

Association of Hypertensive Disorders of Pregnancy With Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-analysis
Maher, et al.

In a meta-analysis of 61 unique articles, this study sought to elucidate the relationship between hypertensive disorders of pregnancy (HDP), autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD) and other neurodevelopmental disorders in offspring. Eleven of the twenty studies on the association of HDP with ASD reported adjusted estimates with a pooled adjusted odds ratio (OR) of 1.35 (95% CI, 1.11-1.64). Six of ten studies on the association of HDP with ADHD reported adjusted estimates with a pooled adjusted OR of 1.29 (95% CI, 1.22-1.36). There was no statistically-significant difference between ASD or ADHD based on the type of exposure (i.e. preeclampsia versus other HDP). This analysis highlights the need for greater surveillance of infants exposed to HDP in order to allow for early intervention that could potentially improve neurodevelopmental outcomes.

Causes of Death After Nonfatal Opioid Overdose
Olfson, et al.

This national longitudinal cohort study of Medicaid beneficiaries between ages 18 and 64 years who experienced nonfatal opioid overdoses between 2001 and 2007 found that during the first year after the nonfatal opioid overdose, the crude death rate was 778.3 per 10,000 person-years and the all-cause

standardized mortality ratio (SMR) was 24.2. The most common immediate causes of death were substance-use associated diseases (26.2%), circulatory system diseases (13.2%), and cancer (10.3%). The SMRs were significantly elevated for drug-use associated diseases, HIV, chronic respiratory diseases, viral hepatitis, and suicide. Suicide was particularly elevated among females in the cohort. This marked excess of deaths in the first year following a nonfatal opioid overdose highlights the importance of closely coordinating substance use, mental health, and medical care for this population.

The Journal of Clinical Psychiatry
Volume 79, Issue 5

A Comprehensive Model of Predictors of Suicide Attempt in Depressed Individuals and Effect of Treatment-Seeking Behavior: Results From a National 3-Year Prospective Study
Hoertel, et al.

The authors sought to develop more effective suicide prevention strategies with this 3-year prospective study of 2,587 participants with DSM-IV criteria for major depressive episode. Structural equation modeling was used to simultaneously examine effects of 4 broad groups of clinical factors previously identified as potential predictors of suicide attempts: (1) severity of depressive illness, (2) severity of psychiatric and other physical comorbidity, (3) sociodemographic characteristics, and (4) treatment-seeking behavior. About 3.5% of the participants attempted suicide during the study. Several factors predicted attempted suicide independently of each other: the absence of treatment-seeking behavior, the severity of the depressive illness (i.e., recurrent thoughts of death, prior suicide attempts, and severity of the general depressive symptom dimension representing the joint effect of most depressive symptoms), and the severity of comorbidities. No sociodemographic characteristics independently contributed to this risk.

Meta-Analysis of the Prevalence of Major Depressive Disorder Among Older Adults With Dementia
Asmer, et al.

This meta-analysis aimed to determine the prevalence and factors associated with depression and dementia. A total of 9,421 studies were screened with 55 meeting inclusion criteria. Results of the data extraction showed that the prevalence of major depressive disorder in all-cause dementia was 15.9% (95% CI, 12.6%–20.1%). The prevalence of MDD was higher among individuals with vascular dementia (24.7%) compared to Alzheimer's disease (14.8%). Prevalence of MDD varied depending on diagnostic criteria used; provisional diagnostic criteria had a prevalence 35.6%, *DSM-III-R* 13.2%, and *DSM-IV* 17.3%.

Effect of Lurasidone on Sexual Function in Major Depressive Disorder Patients With Subthreshold Hypomanic Symptoms (Mixed Features): Results From a Placebo-Controlled Trial
Clayton, et al.

This secondary analysis of a placebo-controlled trial analyzed whether treatment with lurasidone was associated with impairment in sexual functioning in major depressive disorder patients with subthreshold hypomanic symptoms (mixed features). Change in sexual functioning was assessed utilizing the 14-item self-report Changes in Sexual Functioning Questionnaire (CSFQ-14) administered at baseline and week 6 endpoint. Treatment with lurasidone was associated with significant endpoint improvement in CSFQ total scores versus placebo (+5.1 vs +3.1; $P < .05$). Fewer patients treated with lurasidone versus placebo shifted from normal to abnormal sexual function. The proportion of patients with a baseline-to-endpoint shift from normal to abnormal sexual function was smaller for lurasidone versus placebo (1.9% vs 4.3%; CSFQ criteria) at study endpoint. Use of higher lurasidone doses was not associated with greater impairment in sexual functioning. No treatment-emergent adverse events related to sexual function were reported during lurasidone treatment.

The Lancet Psychiatry
Volume 5, Issue 8

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

This RCT aimed to determine whether cognitive behavioural therapy (CBT) is an effective treatment for clozapine-resistant schizophrenia. The authors conducted a pragmatic, parallel group, assessor-blinded, randomized controlled trial in community-based and inpatient mental health services in five sites in the UK. A total of 487 patients with schizophrenia who were intolerant or unresponsive to clozapine were randomly assigned to either CBT (n=242) plus treatment as usual or treatment as usual alone (n=245). The primary outcome was the Positive and Negative Syndrome Scale (PANSS) total score at 21 months and at end of treatment (9 months). Intention to treat analysis was performed on 209 in the CBT group and 216 in the treatment as usual group. No between-group differences occurred in the primary outcome (PANSS total at 21 months, mean difference -0.89, 95% CI -3.32 to 1.55, p=0.48), although the CBT group improved at the end of treatment (PANSS total at 9 months, mean difference -2.40,-4.79 to -0.02; p=0.049).

Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies
Munk-Olsen, et al.

This meta-analysis sought to investigate the association between in-utero lithium exposure and risk of pregnancy complications, delivery outcomes, neonatal morbidity, and congenital malformations. Primary data from pregnant women and their children from six international cohorts based in the community (Denmark, Sweden, and Ontario, Canada) and in the clinics (the Netherlands, UK, and USA) were analyzed. Pregnancies were included for study if they resulted in a liveborn singleton between

1997 and 2015, if health-related information was available for both mother and infant, and if the mother had a mood disorder or had been given lithium during pregnancy. Pregnancies were grouped into lithium-exposed group and a mood disorder reference group. Among 22,124 pregnancies, 727 were eligible for the lithium-exposed group. Among these, exposure was not associated with any of the predefined pregnancy complications or delivery outcomes. An increased risk for neonatal readmission within 28 days of birth was seen in the lithium-exposed group compared with the reference group (pooled prevalence 27.5% [95% CI 15.8-39.1] vs 14.3% [10.4-18.2]; pooled aOR 1.62, 95% CI 1.12-2.33). Lithium exposure during the first trimester was associated with an increased risk of major malformations (pooled aOR 1·71, 95% CI 1·07–2·72), but was not significantly associated with major cardiac malformations (1·54, 0·64–3·70).

Second-generation antipsychotic drugs and short-term mortality: a systematic review and meta-analysis of placebo-controlled randomized trials
Schneider-Thoma, et al.

This systematic review and meta-analysis aimed to assess the contribution of antipsychotic side-effects to reduced life expectancy in individuals with severe mental disorders. A total of 352 studies (comprising 84, 988 participants) with mortality data available constituted the main data set for meta-analysis. Overall, 207 (0·4%) deaths were reported in 53,804 patients on an antipsychotic drug versus 99 (0·3%) deaths in those on placebo. There was no evidence of a difference between antipsychotic drugs and placebo in mortality by any cause (OR 1·19; 95% CI 0·93–1·53), from natural causes (1·29; 0·85–1·94), from suicide (1·15; 0·47–2·81), and from other non-natural causes (1·55; 0·66–3·63). Most subgroup and meta-regression analyses did not indicate any important effect moderators. The exceptions were increased mortality in patients with dementia (OR 1·56; 95% CI 1·10–2·21), in elderly patients (1·38; 1·01–1·89), in aripiprazole-treated patients (2·20; 1·00–4·86), and in studies with a higher proportion of women (regression coefficient 0·025; 95% credible interval 0·010–0·040). For patients with schizophrenia, there was no evidence of an increased mortality risk (OR 0·69; 95% CI 0·35–1·35).

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

Authors sought to evaluate the efficacy of an automated cognitive intervention for fear of heights guided by an avatar virtual coach in virtual reality (VR). The RCT compared a VR program with an automatic coaching feature with usual care in 100 individuals with long-standing fear of heights (mean duration, 30 years). Fear of heights was diagnosed using the Heights Interpretation Questionnaire (HIQ), a 16-item self-report scale. Participants were allocated to usual care or to program involving six 30-minute sessions over 2 weeks. Randomization was stratified by severity of fear of heights. Programming provided gradual exposure to heights but emphasized testing patient-rated cognitive expectations rather than requiring exposure until anxiety was reduced. Attempts were made to eliminate safety-seeking behaviors that might interfere with exposure effects. Overall, VR uptake was extremely high with 47 (96%) of 49 enrollees attending at least one session and 90% completing treatment. At study

end, 69% of the VR group no longer had height phobia, and 78% had a ≥50% improvement, compared with none in usual care. Number needed to treat to at least halve fear of heights was 1.3. Of note, the study was partly funded by the manufacturer, which employed several authors.

Journal of the American Academy of Child and Adolescent Psychiatry Volume 57, Issue 9

Unique Dispositional Precursors to Early-Onset Conduct Problems and Criminal Offending in Adulthood
Pardini, et al.

This longitudinal cohort study using data from the Pittsburgh Youth Study investigated the association between antisocial behavior and childhood interpersonal callousness (IC), negative emotionality (NE), and hyperactivity/impulsivity (HP). First grade boys (n = 256) with high externalizing behaviors were followed semi-annually for 9 assessment waves (between ages ~7-11). Predictors were measured with the Child Behavior Checklist and the Teacher Report Form. Criminal charges were assessed using PA state and FBI records. IC, NE, and HP were positively associated with development of conduct problems. Child conduct problems (but not IC, NE, or HP) were significantly associated with all juvenile offending outcomes. IC was a significant predictor of persistent and violent criminal offending into adulthood into the early 30's. High (upper 10^{th} percentile) IC was associated with higher adult criminal charges (1.6), serious/violent charges (1.7), and arrests (2.7) as compared to moderate (50^{th} percentile) IC. Anxiety problems were inversely associated with both juvenile and adult offending.

Parent Training for Preschool ADHD in Routine, Specialist Care: A Randomized Controlled Trial
Lange, et al.

This multicenter, 2-arm, parallel-group RCT assessed the effect of an evidence-based parent training intervention (New Forest Parenting Programme, NFPP) versus treatment as usual (TAU) on outcomes for preschool children ages 3-7 in the Danish Child and Adolescent Mental Health Services. Children with IQ <70, autism spectrum disorder, in receipt of pharmacologic or psychosocial treatment for ADHD, severe parental psychiatric disorder, or severe social adversity in the home were excluded. Of the study sample (N=164), 88 were randomized to NFPP and 73 to TAU. Assessments were conducted at T1 (baseline), T2 (after treatment), and T3 (36 week follow-up). NFPP was statistically superior to TAU at both T2 and T3 on parental (but not teacher) report of ADHD symptoms (p=.009 and p=0.31), Family Strain Index (p=0.017 and p=0.10), and for parenting efficacy (p=0.004 and p=0.28). There was no improvement in parenting behaviors assessed on direct observation or in child conduct problems.

British Journal of Psychiatry
Volume 213, Issue 2

Diagnosed Depression and Sociodemographic Factors As Predictors of Mortality in Patients with Dementia
Lewis, et al.

The authors of this cohort study sought to investigate depression and sociodemographic factors as predictors of mortality in patients with dementia. Utilizing a UK database of mental health patients from 2008-2016, 4684 patients were identified with an ICD-10 code for dementia. Of those, 247 (7%) also carried a diagnosis of depression as derived by ICD-10 code or natural language processing techniques from free text. Patients were followed for 0.4-14.28 years (mean 3.22; s.d. 2.16). No evidence was found that depression was associated with mortality (adjust hazard ratio 0.94; 95% CI 0.71-1.24). Higher mortality rates were seen in patients who were never married (but not widowed or divorced), lived in deprived areas, demonstrated more cognitive impairment, and were older at the time of dementia diagnosis. Mortality rates were lower in women and Asian patients. There was some weak evidence of a small association between antidepressant use and mortality (adjusted hazard ratio 1.15; 95% CI 1.00-1.33).

Acta Psychiatrica Scandinavica
Volume 138, Issue 2

Long-term antipsychotic polypharmacy prescribing in secondary mental health care and the risk of mortality
Kadra, et al.

This retrospective cohort study investigated the association between long-term antipsychotic polypharmacy use and mortality in patients with serious mental illnesses, and whether this risk varies by cause of death and antipsychotic dose. Long-term antipsychotic polypharmacy was defined as concurrent prescriptions of two or more antipsychotics for six or more months. Using mental health records spanning 8 years, 10,945 individuals with diagnoses of schizophrenia, schizoaffective disorder, or bipolar disorder were included in the study. A weak association was found between antipsychotic polypharmacy with all-cause mortality and with natural causes of death after adjusting for gender and age compared to antipsychotic monotherapy, but this association did not reach statistical significance in the fully adjusted hazard ratios model. No evidence suggested that the dose of antipsychotics affected the risk of death. Overall, there was not enough evidence to determine a clear association between antipsychotic polypharmacy and mortality.