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

Journals Covered:

- * American Journal of Psychiatry (AJP)
- * AJP – Resident’s Journal (RJ)
- * JAMA Psychiatry (JAMA-P)
- * Lancet Psychiatry (LP)
- * Journal of the American Academy of Child & Adolescent Psychiatry (JAACAP)
- * International Journal of Psychoanalysis
- * Miscellaneous: JAMA, Science, NEJM, BMJ.

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Highlights

- Research Watch Commentary: Ziprasidone as Augmentation Agent for Major Depressive Disorder
- High dose pramipexole may be effective for treatment-resistant depression. (AJP)
- Perinatal depression has greater heritability than non-perinatal depression with specific genetic associations. (AJP)
- Higher doses of SSRIs appear to be slightly more effective in the treatment of depression, with the benefit plateauing around 50 mg fluoxetine equivalents. (AJP)
- Immigrants to the USA have a higher rates of psychotic disorders but lower rates of mood, anxiety and substance use disorder compared to natives. (RJ)
- Predisposition for antipsychotic-associated weight gain is associated with activity in the striatal regions of the reward system. (JAMA-P)
- Meta-analysis of blinded RCTs provides little evidence of the superiority of clozapine compared with other second-generation antipsychotics. (JAMA-P)
- CBT as an adjunct to antidepressants is clinically superior to usual care over the long-term for individuals whose depression has not responded to pharmacotherapy. (LP)
- US Preventive Services Task Force (USPSTF) recommends screening for depression in the general adult population, including pregnant and postpartum women. (JAMA)
- Neanderthal alleles in the human genome are correlated with clinically relevant neurological and psychiatric phenotypes in individuals of European descent, particularly depression and mood disorder. (Science)
- Incidence of dementia over three decades in the Framingham Heart Study appears to be declining. (NEJM)
- The risk of suicidality and aggression is increased in children and adolescents during antidepressant treatment. (BMJ)

Research Watch Commentary

Ziprasidone as Augmentation Agent for Major Depressive Disorder

Heather Carey, PharmD, BCPP, Courtney Handy, PharmD Candidate

A study published in the *American Journal of Psychiatry* in December 2015 by Papakostas et al. (1) was the first placebo-controlled trial to test ziprasidone as an augmentation agent with escitalopram in the treatment of major depressive disorder. This randomized, double-blind, placebo-controlled study took place in two 8-week phases: phase 1 being an open-label single-arm trial of escitalopram (average daily dose of escitalopram 20 mg/day; maximum allowable daily dosage 30mg/day) and phase 2 being a double-blinded two-armed study comparing ziprasidone to placebo in augmentation of escitalopram's antidepressant effects (average dose ziprasidone 98 mg/day; maximum allowable 160mg/day). The primary outcome measure was a reduction of $\geq 50\%$ from baseline to endpoint on the Hamilton Rating Scale for Depression (HAM-D score). Remission was considered a HAM-D score ≤ 7 . Secondary outcomes included the Hamilton Rating Scale for Anxiety (HAM-A), the Visual Analog Scale for Pain to test analgesia and anxiolytic effects, as well as QIDS-SR and CGI.

Results revealed a higher clinical response for ziprasidone augmentation than placebo (35.2% versus 20.5%; -3:1 mean decrease in HAM-D; NNT: 7). The NNT is comparable to previous antipsychotic adjunctive antidepressant trials (2). Ziprasidone failed to show significant difference for clinical remission on the HAM-D scale ($p=0.32$) but did for QIDS-SR ($p = 0.02$). Secondary outcomes showed ziprasidone had positive anxiolytic effects but lacked somatic pain relief ($p=0.04$ v. $p=0.46$). The most common adverse effects in the ziprasidone group were somnolence/fatigue, akathisia, and GI upset (33.8%, 15.4%, and 11.2%.)

When critically analyzing the study, several things are to be considered. There was a high drop-out rate for ziprasidone treated patients (31%) however, this was not significantly different from placebo treated patients (21%). While dose adjustment was allowed for intolerable side effects, usage of concomitant agents such as diphenhydramine, propranolol, or increasing doses of benzodiazepines was not permitted which may have lowered discontinuation rates. Exclusion of patients with a high risk of suicidal behavior, severe depressive symptoms, current or past psychotic symptoms, or a diagnosis of substance use disorder within the past 6 months may limit external validity. The open-label lead in phase yielded an unusually low placebo response rate (-3.3 mean HAM-D score) compared to previous adjunctive agent trials. This lead in phase may have increased signal detection at the expense of better efficiency since only 26.1% of the initially enrolled study patients entered the randomization phase. The trial design allowed concomitant use of lithium, buspirone, and benzodiazepines, which may provide anxiolytic and/or antidepressant effects, however, the authors combated this potential source of confounding by ensuring the patients' doses of these agents remained stable throughout phases 1 and 2.

Papakostas et al. study provides evidence to support use of ziprasidone as an additional agent to our current armamentarium for antidepressant augmentation. Ziprasidone's *in vitro* serotonin and

norepinephrine reuptake inhibitory activity as well as its 5HT_{1A} receptor partial agonist activity may play a key role in its efficacy as an augmenting agent. Ziprasidone has a lower incidence of headache, akathisia, and weight gain but a higher incidence of extrapyramidal symptoms compared to aripiprazole (3) and quetiapine (4). Future research could evaluate lurasidone as an augmenting agent due to its similarity in structure and serotonin antagonistic function to ziprasidone. Lurasidone has a quicker time to peak serum concentration (1-3 hours compared to 6-8) and requires smaller meal portions (350 calorie meal) (5).

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The American Journal of Psychiatry

Volume 173, Issue 2

Clinical Experience with High-Dosage Pramipexole in Patients with Treatment-Resistant Depressive Episodes in Unipolar and Bipolar Depression

Fawcett, et al.

In this case series 42 outpatients diagnosed with treatment resistant depression in Major Depressive Disorder or Bipolar Depression were trialed with adjunctive pramipexole that was titrated to effective dosages ranging from 0.75mg to 5mg/day. Of these patients, 76% showed a meaningful clinical response and 24% were either intolerant of the medication or nonresponsive. Remission was achieved by 47.6% of patients and the average dose of response or remission was 2.46 mg/day. The 32 responders were followed for an average of 15.9 months and during that time, 2 subjects relapsed and 7 discontinued pramipexole for various reasons. Side effects associated with pramipexole include nausea, sleep disturbance, anxiety, panic attacks and increased sexual arousal.

Risk of Postpartum Relapse in Bipolar Disorder and Postpartum Psychosis: A systematic Review and Meta-Analysis

Wesseloo, et al.

This meta-analysis found the overall postpartum relapse risk in women with a history of bipolar disorder, postpartum psychosis or both was 35%. Women with bipolar disorder who continued prophylactic medication were less likely to relapse postpartum compared to women who were medication free during pregnancy, 23% and 66% respectively. In women with a history of isolated postpartum psychosis the risk of relapse may be minimized if prophylactic treatment is initiated immediately after delivery which concomitantly reduces in utero exposure.

The Sequential Integration of Pharmacotherapy and Psychotherapy in the Treatment of Major Depressive Disorder: A Meta-Analysis of the Sequential Model and a Critical Review of the Literature

Guidi, et al.

This review found a relative advantage in preventing relapse/recurrence of depression in those who participated in sequential integration of cognitive behavioral therapy and pharmacotherapy compared to control conditions. A significant positive effect was also found for those who participated in CBT during continuation of antidepressant drugs compared to pharmacotherapy alone and those who were randomly assigned to CBT and subsequently had antidepressants tapered and discontinued were significantly less likely to experience relapse.

Heritability of Perinatal Depression and Genetic Overlap with Nonperinatal Depression

Viktorin, et al.

This cohort study of 580,006 patients found the heritability of perinatal depression to be 54% in twin comparisons and 44% in sibling comparisons. The heritability of nonperinatal depression was found to be 32%. One-third of genetic contributions found were specific to perinatal depression and not found in nonperinatal depression, suggesting perinatal depression may be its own subset of depression.

Systematic Review and Meta-Analysis: Dose Response Relationship of Selective Serotonin Reuptake Inhibitors in Major Depressive Disorder

Jakubovski, et al.

This meta-analysis found that there is a small but statistically significant positive association between SSRI dose and efficacy and that higher doses of SSRIs appear to be slightly more effective in the treatment of major depressive disorder. This benefit plateaus at around 250 mg imipramine equivalents (50 mg of fluoxetine.) However, the benefit of higher dosages is offset by the decreased tolerability.

Longitudinal Psychiatric Symptoms in Prodromal Huntington's Disease: A Decade of Data

Epping, et al.

This longitudinal study followed 1,007 study participants carrying the Huntington's disease mutation and 298 controls and found 19 out of 24 psychiatric measures were significantly higher at baseline and showed significant increases longitudinally in those carrying the mutation compared to controls. Higher symptom ratings were more often reported by companions than by those carrying the mutation. This suggests that psychiatric manifestations develop more often than previously thought in the Huntington's disease prodrome and often those affected by the disease demonstrate decreasing awareness regarding these psychiatric symptoms.

The American Journal of Psychiatry - Resident's Journal

Volume 11, Issue 2

Immigration and Risk of Psychiatric Disorders: A Review of Existing Literature

Shekunov J

This article reviews literature on the relationship between psychiatric illness and immigration. Immigrants to the United States generally have lower rates of mood, anxiety, and substance use disorders compared to the U.S.-born population, with increasing risk of psychiatric illness with longer duration of residence in the United States and generational status. Immigrant groups from across the world have higher rates of psychotic disorders compared to natives, with risk persisting into the second generation. The author suggests that when providers are assessing immigrant patients, special consideration should be given to pre-migration, migration, and post-migration factors.

Undocumented Immigrants in Psychiatric Wards

Wei, et al

This case report depicts a 23-year-old undocumented Honduran male who was brought in by EMS to the ED after he was found agitated in an apparent manic episode breaking into a car without a shirt on in the middle of winter. After inpatient psychiatric treatment, the patient did express desire to return to Honduras, however the patient's lack of documentation prolonged his repatriation by 6 weeks with a hospital stay of \$281,000. The US has spent roughly \$2 billion per year on the health care of undocumented immigrants. Laws guiding the care of patients in the emergency department require stabilization of patients independent of legal status and hospitals cannot discharge patients without an appropriate plan. Without clear laws governing the management of undocumented patients, hospitals have been repatriating patients without legal oversight, making undocumented patients vulnerable to abuse and unethical conduct.

JAMA Psychiatry

Volume 73, Issue 2

Heterogeneity of Psychosis Risk Within Individuals at Clinical High Risk - A Meta-analytical Stratification

Fusar-Poli, et al.

This meta-analysis showed that the risk for psychosis varies even in people who are clinical high risk for psychosis. The risk in those with brief limited intermittent psychotic symptoms (BLIPS) is greater than those with attenuated psychotic symptoms (APS). Another clinical high risk subgroup, entitled the genetic risk and deterioration syndrome group (GRD), was found to be rare and not associated with an increased risk of psychosis.

Striatal Reward Activity and Antipsychotic-Associated Weight Change in Patients with Schizophrenia

Nielsen, et al.

In order to determine if attenuated striatal activity during reward anticipation is associated with amisulpride-induced weight change in antipsychotic-naive patients with schizophrenia, a group of antipsychotic naive patients were given 6 weeks of the D2 antagonist amisulpride, with fMRI and weight monitoring before and after treatment. Activity in the striatal regions of the reward system was found to be associated with the individual variability in the predisposition for antipsychotic-associated weight gain. Weight gain was predicted by low baseline reward-related activity in the right-sided putamen. After 6 weeks, weight gain was associated with an increase in reward activity in the same region during treatment.

Association of Age at Menopause and Duration of Reproductive Period With Depression After Menopause - A Systematic Review and Meta-analysis

Georgakis, et al.

This study showed that longer exposure to endogenous estrogens, expressed as older age at menopause and longer reproductive period, is associated with a lower risk of depression later in life. Menopause at age 40 years or more compared with premature menopause was associated with a 50% decreased risk for depression.

Association of Mental Disorders with Subsequent Chronic Physical Conditions: World Mental Health Surveys From 17 Countries

Scott, et al.

Study investigated associations between 16 temporally prior DSM-IV mental disorders with subsequent onset or diagnosis of 10 chronic physical conditions (eg, heart disease, stroke, diabetes mellitus, HTN, chronic lung disease, chronic pain). Face-to-face, cross-sectional household surveys were conducted in 17 countries over 9 years in which lifetime prevalence and age of onset of DSM-IV mental disorders were retrospectively assessed. Results showed that mood, anxiety, substance use, and impulse control disorders were significantly associated with most of the chronic physical conditions (asthma and cancer being the lowest with chronic lung disease and chronic pain the highest). Findings suggest that mental disorders of all kinds are associated with the increased risk of onset of a wide range of chronic physical conditions. [Intriguingly the study did not comment on schizophrenia spectrum disorders.]

Frontal Glutamate and γ -Aminobutyric Acid Levels and Their Associations with Mismatch Negativity and Digit Sequencing Task Performance in Schizophrenia

Rowland, et al.

Study investigates the association between glutamate levels and auditory mismatch negativity (biomarker for schizophrenia), which is thought to reflect NMDA receptor function. 53 control patients were compared to 45 patients with Schizophrenia using EEG, magnetic resonance spectroscopy for glutamate and GABA, and an assessment of verbal working memory. Results found mismatch negativity amplitude and glutamate were reduced in the schizophrenia group. Smaller MMN amplitude was linked to lower glutamate level and higher ratio of glutamine to glutamate which was correlated to poor verbal working memory in the schizophrenia group.

JAMA Psychiatry. Online First.

Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis

Samara, et al.

Published online February 03, 2016. doi:10.1001/jamapsychiatry.2015.2955

This is a meta-analysis of published and unpublished single- and double-blind RCTs in treatment-resistant schizophrenia (any study-defined criterion) that compared any antipsychotic (at any dose and in any form of administration) with another antipsychotic or placebo. The most surprising finding is that in contrast to unblinded, randomized effectiveness studies, blinded RCTs provide little evidence of the superiority of clozapine compared with other second-generation antipsychotics. Accompanying editorial by Kane & Correll discusses the results of the study, and raise concerns regarding the generalizability of the samples that were enrolled into the blinded RCTs.

The Lancet Psychiatry

Volume 3, Issue 2

Antidepressant augmentation with metyrapone for treatment-resistant depression (the ADD study): a double-blind, randomised, placebo-controlled trial

McAllister-Williams, et al.

In this double-blind, randomized, placebo-controlled trial, patients with treatment-resistant depression on antidepressant treatment were randomly assigned to metyrapone (antiglucocorticoid agent) or placebo in addition to existing regimen. Primary outcome was improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) score 5 weeks after randomization. No significant difference in MADRS scores was found between metyrapone and placebo at the end of 5 weeks.

Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBaIT randomised controlled trial

Wiles, et al.

The CoBaIT randomized controlled trial shows that CBT as an adjunct to usual care that includes antidepressants is clinically effective and cost effective over the long-term for individuals whose depression has not responded to pharmacotherapy. Subjects who had substantial depressive symptoms after at least 6 weeks of antidepressant therapy were randomized to usual care or usual care plus CBT. Long term outcomes were assessed at 3-5 year follow-up. On average intervention group had 4.7 points lower on Beck Depression Inventory compared to usual care, had fewer anxiety symptoms, and were twice as likely to meet criteria for response or remission.

Journal of the American Academy of Child and Adolescent Psychiatry

Volume 55, Issue 2

Associations Between Peer Victimization and Suicidal Ideation and Suicide Attempt During Adolescence: Results From a Prospective Population-Based Birth Cohort

Geoffroy, et al.

The main objective of this study was to assess whether adolescents who are victimized by peers were at increased risk for suicidal ideation and suicide attempt. Compared to individuals who had not been victimized, victims reported higher rates of suicidal ideation at age 13 and suicide attempt at age 15. Victimization by peers at age 13 predicted suicidal ideation and suicide attempt two years later, regardless of baseline suicidality, mental health problems, and other confounding factors. In addition, the longer the period of victimization, the greater the risk.

Autism Spectrum Disorders and Other Mental Health Problems: Exploring Etiological Overlaps and Phenotypic Causal Associations

Tick, et al.

This twin study examined the etiological overlap between the diagnosis of autism spectrum disorder and emotional symptoms, hyperactivity, and conduct problems measured with the Strength and Difficulties Questionnaire. More than 50% of twins with broad spectrum/autism spectrum disorder met borderline/abnormal levels cut-off criteria for emotional symptoms or hyperactivity and approximately 25% met criteria for the three concerns. There was a moderate genetic correlation between autism spectrum disorder and emotional symptoms. In regards to conduct problems, nonshared-environmental factors had the greatest impact.

Clinical Correlates of Hoarding With and Without Comorbid Obsessive-Compulsive Symptoms in a Community Pediatric Sample

Burton, et al.

This study assessed the prevalence and clinical correlates of hoarding, with and without obsessive compulsive (OC) symptoms in a community based pediatric sample. Using the Toronto Obsessive-Compulsive Scale (TOCS), the authors measured hoarding and OC symptoms in over 16,000 youth between the ages of 6 and 17. Individuals were divided into four groups based on the presence or absence of OC symptoms and hoarding. These four groups were compared on parent-or-self-reported medical and psychiatric conditions, anxiety symptoms measured with the Child Behavior Checklist, and attention-deficit/hyperactivity disorder (ADHD) symptoms. In this community sample, hoarding symptoms occurred in both the presence and absence of obsessive-compulsive symptoms. Inattentive symptoms of ADHD were more common in the individuals with only hoarding symptoms. In addition, the hoarding only group demonstrated fewer anxiety symptoms.

Severity of Cortical Thinning Correlates with Schizophrenia Spectrum Symptoms

Watsky, et al.

The study examined a total of 66 siblings of patients with childhood-onset schizophrenia (COS) for symptoms of schizophrenia spectrum personality disorders (avoidant, paranoid, schizoid, schizotypal). Structural MRI scans were obtained at 2-year intervals from the siblings and from 62 healthy volunteers.

Results indicate that cortical thinning correlated with symptoms of schizotypal and to a lesser extent, schizoid personality disorder. The left temporal and parietal lobes showed the most amount of thinning. Longitudinal thinning trajectories were found not to differ between siblings and healthy volunteers.

International Journal of Psychoanalysis

Psychic reality and the nature of consciousness

Fonagy & Allison

Published online before print. doi: 10.1111/1745-8315.12403

Fonagy and Allison investigate a psychoanalytically-informed conceptualization of consciousness. Using clinical material from a patient who had disturbances in consciousness, the authors consider consciousness as a developmental process in addition to being a perceptual modality.

Miscellaneous

Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement

Siu AL; and the US Preventive Services Task Force (USPSTF)

JAMA.

2016;315(4):380-387. doi:10.1001/jama.2015.18392.

US Preventive Services Task Force (USPSTF) recommends screening for depression in the general adult population, including pregnant and postpartum women. The USPSTF found adequate evidence that programs combining depression screening with adequate support systems in place improve clinical outcomes (i.e., reduction or remission of depression symptoms) in adults, including pregnant and postpartum women.

The phenotypic legacy of admixture between modern humans and Neandertals

Simonti, et al.

Science

Feb 2016: Vol. 351, Issue 6274, pp. 737-741

DOI: 10.1126/science.aad2149

Non-African humans are estimated to have inherited on average 1.5 to 4% of their genomes from Neanderthals. Researchers combined genotyping data with electronic health records, and discovered that individual Neanderthal alleles were correlated with clinically relevant neurological, psychiatric, immunological, and dermatological phenotypes in individuals of European descent. In particular,

Neanderthal alleles together explained a significant fraction of the variation in risk for depression and mood disorders.

Incidence of Dementia over Three Decades in the Framingham Heart Study

Satizabal, et al.

New England Journal of Medicine

February 2016; 374:523-532

Authors describe temporal trends indicating a decline in the incidence of dementia over three decades among participants in the Framingham Heart Study. Relative to the incidence of dementia during the first epoch (late 1970s - early 1980s), the incidence declined by 22%, 38%, and 44% during the second, third, and fourth epochs (late 2000s - early 2010s), respectively.

Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports

Sharma, et al.

BMJ

Jan 2016;352:i65

doi: <http://dx.doi.org/10.1136/bmj.i65>

In this systematic review and meta-analysis, data from double blind placebo controlled trials of duloxetine, fluoxetine, paroxetine, sertraline, and venlafaxine was studied. In adults there was no significant increase in the four outcomes of mortality, suicidality, akathisia and aggression, but in children and adolescents the risk of suicidality and aggression approximately doubled with odds ratios of 2.39 (95% CI 1.31 to 4.33) and 2.79 (95% CI 1.62 to 4.81) respectively.

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- Up to 5 references are allowed. References should be in Vancouver style.
- No abstract is required.
- Title Page should contain: Title, Author information and affiliation, word count, declaration of conflict of interest.
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