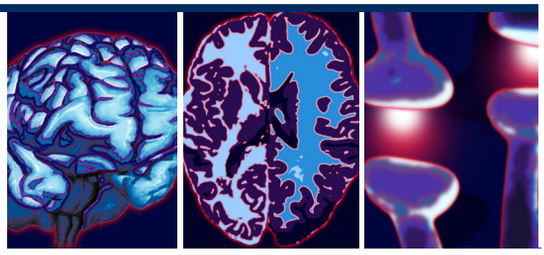
JOURNAL WATCH



Our experts highlight the most important research articles across the spectrum of topics relevant to the field of neuropsychiatry

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Fiedorowicz JG, Endicott J, Leon AC, Solomon DA, Keller MB, Coryell WH: Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder.
***Am. J. Psychiatry* 168, 40–48 (2011).**

Prospective cohort studies of individuals with a baseline diagnosis of major depression show rates of diagnostic conversion to bipolar disorder (BPD) of approximately 10–20% (range: 4.0–48.6%). Extending work published over 15 years ago from the National Institute of Mental Health Collaborative Depression Study (CDS), Fiedorowicz *et al.* report on a cohort of 550 individuals with an initial diagnosis of major depression based on Research Diagnostic Criteria (RDC) who were followed for a mean of 17.5 years (up to 31 years). Nearly one fifth of subjects (19.6%) met criteria for BPD during follow-up: most for bipolar II (12.2%) and a smaller proportion bipolar I (7.5%). Subthreshold hypomania at intake was a significant predictor of BPD at follow-up with each manic symptom contributing an increased risk of diagnostic conversion of 29%. Decreased need for sleep, unusually high energy and increased goal-directed activity at baseline were specifically predictive of BPD. As predictors of BPD, the presence at baseline of more than three manic symptoms was associated with a specificity of 95%, although with a low sensitivity (16%) and positive predictive value (42%). Other baseline factors associated with conversion to BPD included age, earlier age of illness onset, marital status (single), delusions and family history of bipolar I or II. Although limited by its naturalistic design, which did not control for antidepressant or other treatment, this study importantly extends previous work in two respects. It confirms an appreciable rate of diagnostic conversion from unipolar major depression to BPD and suggests that, while the presence of subclinical hypomanic symptoms at baseline is inadequate alone for predicting BPD, it should prompt close monitoring during follow-up, particularly in the setting of younger age, earlier age of depression onset, bipolar family history and psychotic symptoms.

Torres AR, Ramos-Cerqueira AT, Ferrao YA, Fontenelle LF, Conceicao do Rosario M, Miguel EC: Suicidality in obsessive–compulsive disorder: prevalence and relation to symptom dimensions and comorbid conditions.
***J. Clin. Psychiatry* 72(1), 17–26 (2011).**

In the largest clinical study to evaluate the prevalence and clinical correlates of suicidality in obsessive–compulsive disorder (OCD), Torres *et al.* report on 582 outpatients with primary OCD who were recruited through the Brazilian Research Consortium on Obsessive–Compulsive Spectrum Disorders. Comorbidity was common in this sample with nearly two-thirds meeting *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria for major depressive

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disorder (MDD), over a third for impulse control disorders (e.g., trichotillomania, skin picking and kleptomania), over a quarter for tic disorders and over an eighth for post-traumatic stress disorder (PTSD). Of the total OCD sample, 11% had previously attempted suicide while 20.1% had previously planned suicide. Lifetime suicidal thoughts were reported by 36%, while one in ten endorsed current suicidal thoughts. A total of 16% had a completed suicide in the family. On univariate analysis, suicidal thoughts and plans were associated with higher scores on the obsession subscale of the Yale–Brown Obsessive Compulsive Scale (YBOCS), although the mean YBOCS total score and compulsion subscale score were not associated with suicidality. In the multivariate analysis OCD symptoms of a sexual/religious nature as well as comorbid substance use disorders were associated with both suicidal thoughts and plans, while impulse control disorders were associated with current suicidal thoughts as well as lifetime suicide plans and attempts. Among axis I disorders, only MDD and PTSD were independently associated with all four aspects of suicidality assessed (current and lifetime thoughts, lifetime plans and lifetime attempts). Lower social class, having no children, having no religious practice and marital status (single) were also associated with aspects of suicidality. Limitations of this study include its cross-sectional design, lack of assessment for personality disorders, the relatively small number of participants with suicide attempts, and reliance on retrospective self-reporting. Nevertheless, this study indicates that suicidal thoughts and behaviors are common in OCD and deserve close evaluation, particularly among those patients with symptoms of a sexual/religious nature and with comorbid MDD, PTSD, substance use or impulse control disorders.

Holsen LM, Spaeth SB, Lee J-H *et al.*: Stress response circuitry hypoactivation related to hormonal dysfunction in women with major depression. *J. Affective Disord.* DOI: 10.1016/j.jad.2010.11.024 (2011) (Epub ahead of print).

Various hypotheses have been advanced for the 2:1 female preponderance in major depressive disorder (MDD) including psychiatric comorbidity, gender role and neuroendocrine factors. This functional MRI study involving blood oxygen level-dependent signal changes in response to stressful visual stimuli investigated the relationship between hypothalamic–pituitary–gonadal axis hormones and stress response circuitry dysfunction in ten women with recurrent or chronic MDD, currently in remission, compared with ten healthy matched controls. Subjects were scanned during the late follicular/mid-cycle menstrual phase (days 10–15) while viewing a set of pictures that were negative (unpleasant)/high arousal or neutral/low arousal. There were no differences between the MDD and control group on state mood or anxiety pre-/postscanning. However, functional MRI results showed greater blood oxygen level-dependent signal intensity changes between negative and neutral stimuli conditions in controls versus MDD subjects in the hypothalamus, amygdala, hippocampus, orbital frontal cortex, anterior cingulate cortex (ACC) and subgenual ACC. MDD women had lower serum estradiol and higher serum progesterone levels compared with controls. Hypoactivations in the hypothalamus, subgenual ACC, amygdala and orbital frontal cortex in MDD were associated with low estradiol and high progesterone and remained significant after eliminating four MDD subjects on antidepressants from the analysis. Although limited by a small number of subjects and no assessment of adrenal status, which may affect gonadal function, this preliminary study suggests that hypoactivation of the stress response circuitry in women with MDD currently in remission is associated with dysregulation of the hypothalamic–pituitary–gonadal axis. These findings provide initial evidence that hormonal dysregulation and brain activity deficits in response to stress contribute to trait characteristics in women that may, in part, underlie vulnerability to MDD.

Robb AS, Cueva JE, Sporn J *et al.*: Sertraline treatment of children and adolescents with posttraumatic stress disorder: a double-blind placebo-controlled trial. *J. Child Adolesc. Psychopharmacol.* 20(6), 463–471 (2010).

The neurobiological basis for childhood post-traumatic stress disorder (PTSD) is not well understood. In the adult literature, it has been suggested that traumatic stress is neurotoxic and may be associated with deficits in hippocampal function and reduction in hippocampal volume. Sertraline and other selective serotonin reuptake inhibitors have been shown, in animal models, to counteract the toxic effects of stress on the hippocampus as well as enhance neurogenesis. It is still uncertain whether or not we can extrapolate this data to children and adolescents and the developing brain.

To date, two 12-week open-label trials of citalopram in the treatment of PTSD reported a 50% or greater reduction in symptom severity for a total of 32 children and adolescents between both studies. A different study (n = 24) compared cognitive behavioral therapy with or without sertraline. In this study, for the treatment of PTSD, sertraline augmentation was not associated with significantly greater improvement compared with cognitive behavioral therapy alone. This study is the first large, double-blind, randomized, placebo-controlled trial designed to evaluate the safety and efficacy of a selective serotonin reuptake inhibitor in children and adolescents with PTSD. Children and adolescents between the ages of 6 and 17 years were randomized to 10 weeks of treatment with sertraline (50–200 mg/day) or placebo. The primary efficacy measure was the University of California, Los Angeles Post-Traumatic Stress Disorder Index (UCLA PTSD-I). A total of 131 patients were randomized to sertraline (n = 67; female: 59.7%; mean age: 10.8 years) or placebo (n = 62; female: 61.3%; mean age: 11.2 years). There was no difference between sertraline and placebo in mean change in the UCLA PTSD-I score or on

last observation carried forward analysis. Discontinuation due to adverse events was higher in the sertraline group (7.5%) compared with placebo (3.2%). Sertraline treatment was not associated with any change in weight or any clinically significant change in ECG or laboratory values. Various explanations for these results must be taken into consideration. An unusually high placebo response rate could have influenced this outcome. Alternatively, given that the neurobiological correlates of childhood PTSD are not sufficiently understood, sertraline could simply lack efficacy in childhood PTSD. Lastly, there could have been methodological flaws in this study, influencing these results. In any case, the findings suggest that the positive results from adult trials may not be generalizable to childhood PTSD and further research is recommended.

Wilens TE, Martelon M, Fried R *et al.*: Do executive function deficits predict later substance use disorders among adolescents and young adults? *J. Am. Acad. Child Psychiatry* 50(2), 141–149 (2011).

Cognitive and neuropsychological disturbances have been implicated in the development of substance use disorders (SUDs). One disorder with neurobiological disturbances that has been continually associated with SUDs in the literature is attention-deficit/hyperactivity disorder (ADHD). It has been suggested that this link may be due to executive function deficits (EFDs) since EFDs are common in persons with ADHD. There would be much relevance to public health, clinical and research arenas if EFDs were, in fact, found to moderate the risk for SUD in children with and without ADHD.

Therefore, this study evaluated whether EFDs affect the risk for SUD in children with ADHD by looking at longitudinal case–control samples of aging boys and girls. It also examined if EFDs increase the risk for SUD in subjects without ADHD. Subjects were assessed at 5-year follow-up and again 4–5 years later. A total of 435 subjects were evaluated (232 subjects with ADHD and 203 controls; the mean age in both groups was approximately 16 years). At the final follow-up period, ADHD was found to be a significant predictor of stable cigarette smoking and SUD into late adolescence and young adult years, as has been shown in many other studies. However, it did not appear that executive function (EF) within ADHD accounted for earlier onset of SUD or increased risk for SUD. In fact, EFDs were not associated with an increase in subsequent substance use outcomes, in patients with or without ADHD. It is clear from this study that abnormal results on tests of neuropsychological function indicative of EF may not predict SUD. These results suggest that other factors are accounting for SUD in ADHD samples. These factors could be non-neuropsychologically derived EF-related symptoms, functional impairment or non-EF factors. Importantly, this study found that children and adolescents who do not smoke, have a SUD or EFD who then start smoking during the 5-year interval in the study, were at an increased risk for subsequent EFD. The idea that new-onset cigarette smoking may predispose individuals to the development of EFD is incredibly concerning and should be evaluated further. Lastly, this study found decreased risk of drug use disorders among ADHD subjects with EFD. The implications and causality of this are unclear. It is possible that these children undergo more parental monitoring given their EFDs or that they are less socially accepted and therefore are not exposed to drugs of abuse as frequently. Again, this is another area that requires further examination.

Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V: Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch. Gen. Psychiatry* 68(2), 128–137 (2011).

Although progressive brain atrophy in schizophrenia is thought to reflect an underlying and intrinsic neuropathological process, animal studies suggest that antipsychotics may contribute to this phenomenon. Since antipsychotics are prescribed for long periods in the treatment of schizophrenia, mood and anxiety disorders, it is important to examine the possibility of antipsychotic-associated brain tissue loss and, consequently, establish the risk:benefit ratio associated with these drugs more clearly.

In an attempt to elucidate this issue, Ho *et al.* examined the contributions of illness duration, antipsychotic treatment, illness severity and substance abuse in the brain volumes of 211 patients with schizophrenia who underwent repeated neuroimaging soon after illness onset. On average, each patient had three scans (≥2 and as many as 5) over 7.2 years (up to 14 years). Greater intensity of antipsychotic treatment (chlorpromazine milligram equivalents per day) was associated with generalized and specific brain tissue reductions even after controlling for effects of the other potential predictors. Of note, an enlarged putamen was associated with higher doses of both typical and nonclozapine atypical antipsychotics.

By showing that antipsychotics have a subtle but measurable influence on brain tissue loss over time, this study highlights the need to continuously assess the risk:benefit ratio associated with these drugs. It suggests that clinicians should prescribe the minimal amount of antipsychotics needed to achieve a response and add psychosocial and rehabilitation strategies to improve outcomes more often. It also shows that further research should be done to synthesize new antipsychotic medications with different mechanisms of action and more favorable cost:benefit ratios.

Wüstenberg T, Begemann M, Bartels C *et al.*: Recombinant human erythropoietin delays loss of gray matter in chronic schizophrenia. *Mol. Psychiatry* 16(1), 26–36 (2011).

Follow-up MRI studies show progressive brain tissue loss in patients with

schizophrenia. Unfortunately, no treatment exists to counteract this slowly progressive phenomenon. Originally established for the treatment of anemia, recombinant human erythropoietin (EPO) was shown to cross the blood–brain barrier, to possess multifaceted direct neuroprotective properties in different animal models of stroke and to be well tolerated clinically.

In a placebo-controlled study including 32 male patients with schizophrenia randomized for either weekly high-dose EPO for as little as 3 months (n = 16) or placebo (n = 16), Wüstenberg *et al.* have shown, through voxel-based morphometry, that the active drug interrupted the progressive atrophy in the hippocampus, amygdala, nucleus accumbens and neocortex. More specifically, gray matter protection was highly associated with cognitive improvement in attention and memory levels. These findings suggest that EPO is effective against neuroprogressive loss of brain tissue in schizophrenia, and that follow-up studies to optimize EPO dose and duration of treatment should be pursued in this population. Provided that these results can be consolidated in a larger clinical trial, EPO would be the first compound for prevention of cortical gray matter loss and improvement of neurocognition.

Grob CS, Danforth AL, Chopra GS *et al.*: Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch. Gen. Psychiatry* 68(1), 71–78 (2011).

From the late 1950s to the early 1970s, research explored the clinical use of hallucinogens to treat the existential anxiety, despair and isolation associated with terminal cancer. Psilocybin, a substance that occurs in nature in various species of mushrooms, is rapidly metabolized to psilocin, which is a potent agonist of serotonin 5-$HT_{1A/2A/2C}$ receptors. Recent data suggest that psilocybin is not hazardous to physical health.

After more than 35 years of lack of interest in its therapeutic properties, Grob *et al.* performed the first study examining the efficacy of psilocybin in 12 patients with anxiety and end-stage cancer. A total of 12 subjects with different *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV anxiety disorder diagnoses (e.g., acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer or adjustment disorder with anxiety) and different types of advanced cancer (including breast, colon, ovarian, peritoneal and salivary cancer, and multiple myeloma) were included in a double-blind, placebo-controlled study of a moderate dose (0.2 mg/kg) of psilocybin with subjects acting as their own control.

Subjects tolerated the treatment sessions physiologically and psychologically, without severe anxiety or a 'bad trip' (e.g., psilocybin led to only modest effects on the anxious ego dissolution scale of 5D Altered States of Consciousness profile). The State-Trait Anxiety Inventory trait anxiety subscale showed a significant anxiety reduction at 1 and 3 months after treatment. The Beck Depression Inventory revealed an improvement of mood that reached significance at 6 months; the Profile of Mood States identified mood improvement after treatment with psilocybin that approached, but did not reach, significance. These results support the need for more research in this long-neglected field.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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