

PSYCHIATRY ALERTS NOS

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Predicting Bipolar Conversion

According to the results of a cohort study, the strongest predictor of conversion from unipolar depression to bipolar depression is a parental history of bipolar disorder. Other significant predictors include psychotic depression at the index episode, emergency or inpatient treatment of the index episode, and prior or concurrent nonaffective psychosis.

Background: The occurrence of the first episode of hypomania, mania, or mixed symptoms in a patient with depression signals conversion to bipolar disorder and should prompt modifications in treatment. However, detection of this conversion is often clinically delayed and results in long periods of untreated bipolar disorder, which are known to negatively affect outcomes. The current historical prospective cohort study was undertaken to confirm previously identified risk factors in a large representative patient sample.

Methods: Using data from linked Danish civil and psychiatric registries, a cohort of >91,000 patients with a first diagnosis of unipolar major depression between 1995 and 2016 were identified. Conversion to a diagnosis of bipolar depression during the follow-up period, which began 8 weeks after the index episode, was the primary outcome. Based on previous research, the following clinical predictors for conversion were evaluated: gender; age at onset; treatment setting of the index depressive episode; characteristics of the index episode (i.e., severity, presence of psychotic symptoms, recurrent vs single episode); concomitant mental health diagnoses; and parental mental health disorders.

Results: The study cohort (n=91,587) had a mean age of 31 years at the index depressive episode, and 63% of patients were female. Most (57%) received treatment as outpatients, and nearly 40% had a concomitant psychiatric diagnosis. Parental history of psychiatric disorder was present in 27% of the cohort. The mean duration of follow-up was 8 years.

During follow-up, a total of 3910 patients experienced conversion to bipolar depression, making the overall cumulative incidence of conversion 8.4%. Risk was greatest during the first year after unipolar depression diagnosis. The strongest predictor of conversion was parental history of

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bipolar disorder (adjusted hazard ratio [HR],* 2.6). Other significant predictors with similar HRs included presence of psychotic depression at the index episode (HR, 1.73), presence of prior or concurrent nonaffective psychosis (HR, 1.73), and inpatient treatment of the index episode (HR, 1.76). Additional predictors with smaller but still statistically significant hazard ratios included female gender; emergency room treatment of the index episode; recurrent depression; at least moderate severity of the index episode; prior or current alcohol abuse; and parental history of unipolar depression. Despite other evidence suggesting risk is greater in young patients, age at diagnosis was not associated with conversion in this sample, possibly because registry-based studies may underestimate the conversion rate in pediatric populations.

Discussion: Based on the findings in this large, nationally representative sample, presence of severe, recurrent, or psychotic depression, comorbid alcohol abuse, and need for inpatient treatment appear to be clinically relevant predictors of conversion to bipolar depression in patients initially treated for unipolar depression. Early detection of at-risk patients could reduce the duration of untreated bipolar illness.

Musliner K, Ostergaard S: Patterns and predictors of conversion to bipolar disorder in 91587 individuals diagnosed with unipolar depression. *Acta Psychiatrica Scandinavica* 2018;137 (May):422–432. From Aarhus University; and the Lundbeck Foundation, Aarhus, Denmark. **Funded by the Lundbeck Foundation; and Aarhus University. The authors declared no competing interests.**

*See Reference Guide.

Evaluating Mental Health Apps

At least 10,000 smartphone apps now exist that target mental health, but there are no available tools that provide a reliable method of evaluating their safety or usefulness.¹ The American Psychiatric Association (APA) has created a rubric to guide clinicians in the evaluation of these apps. The rubric does not directly rate or score an app, and it does not rely on any existing user ratings. Rather, it suggests that clinicians and/or patients consider a simple 5-step evaluation process, progressing to the next stage only if the app satisfies the clinical need at the current stage. There are no specific criteria to judge whether an app is satisfactory at each hierarchical step. Instead, the APA framework includes a series of questions intended to guide a personalized determination of the appropriateness of an app for a given patient. The specific questions are available on the APA website at <https://psychiatry.org/psychiatrists/practice/mental-health-apps/app-evaluation-model>.

Step 1: Prior to evaluating an app, the clinician should gather as much useful background information as possible. Pertinent information at this stage could include the developer, cost to the patient, number of updates, and available platforms.

Step 2: Privacy and digital safety/risk should be evaluated next. At this stage, the privacy policy for the app should be carefully assessed to determine such things as: what data are collected; is data personally identifiable; can a user opt-out of data collection; what data are shared and with whom; where is the data stored; and what security measures are in place.

Step 3: If the digital safety of the app is acceptable, evidence for the effectiveness of the app should be evaluated. While some apps have documented clinical-trial efficacy, many do not. If no such evidence is found, the clinician should consider downloading and testing the app personally. User feedback may be helpful at this stage.

Step 4: If in the previous steps it was determined that the app offers minimal risk in terms of digital safety and privacy and appears to offer some benefit, ease of use can be assessed. Specific questions here could include: is the app customizable, easy to use, and culturally sensitive; and is it accessible to those with a disability.

Step 5: The final step in the hierarchy is evaluation of interoperability, specifically whether the patient and clinician can share and discuss data or feedback from the app so as not to fragment care. While this may not be relevant to all apps, it may be especially important for those that monitor mood or address medication management.

In an effort to better understand how clinicians use the model and to gather data to be used for further improvement, the APA is encouraging users to share their app evaluations on the APA Web site.²

¹Torous J, Chan R, Gipson S, Kim J, et al: A hierarchical framework for evaluation and informed decision making regarding smartphone apps for clinical care. *American Journal of Psychiatry* 2018; doi 10.1176/appi/ps.201700423. From Harvard Medical School, Boston, Mass; and other institutions. **The authors declared no competing interests.**

²American Psychiatric Association. App evaluation model Web site. <https://psychiatry.org/psychiatrists/practice/mental-health-apps/app-evaluation-model>. Accessed April 18, 2018.

Brain Morphology and Depression Relapse

A longitudinal neuroimaging study identified a distinct pattern of changes associated with relapse in patients with depression, including structures involved in regulation of emotion.¹

Methods: Study participants were 60 patients with major depressive disorder and 54 age- and gender-matched healthy controls. When enrolled, all patients were experiencing a moderate or severe depressive episode requiring inpatient treatment. Patients were divided into 2 groups based on the clinical course over the subsequent 2 years: 37 patients who experienced ≥ 1 relapse episode and 23 patients who were relapse-free. Full remission, defined as absence of symptoms for ≥ 2 months, was required before diagnosing a relapse. All patients and controls underwent brain MRI scans at study entry and 2 years later. The analysis included both gray matter volume and region-of-interest cortical thickness of the insula, medial orbitofrontal cortex (OFC), rostral anterior cingulate cortex (ACC), and rostral middle frontal gyrus. Additional analyses investigated the potential influences of medication and depression severity at follow-up.

Results: Patients and controls were in their mid-30s on average. Medication exposure, both at baseline and during follow-up, did not differ between patients who did or did not relapse. However, patients who experienced a relapse had significantly higher baseline gray matter volumes than patients without relapse (in the dorsolateral prefrontal cortex [DLPFC] only) and controls (in both the DLPFC and insula). Longitudinal whole-brain analysis identified a significant increase in gray matter volume in healthy controls ($p < 0.001$), a decrease in patients who relapsed ($p = 0.04$), and no significant change in relapse-free patients. In the rostral middle frontal gyrus, an area chosen to represent the DLPFC, patients with relapse had a significant decrease in gray matter volume ($p < 0.001$), but those without relapse and healthy controls showed no change. Neither medication status nor depression severity was associated with gray matter volumes or changes.

Longitudinal region-of-interest analysis showed significant increases in cortical thickness in the left medial OFC and left rostral ACC in patients without relapse ($p = 0.003$ and $p = 0.005$, respectively). Healthy controls also showed increases in both of these areas, while relapsed patients did not. Patients with relapse, but no other group, had a decrease of cortical thickness in the right rostral middle frontal gyrus.

Discussion: The changes observed in these patients are consistent with neurobiological models of major depressive disorder that assume a dysfunction of the frontolimbic brain circuitry. They also extend previous cross-sectional data to a non-elderly population of patients with depression and appear to be the first to account for effects of medication. While there were unexpected findings that remain unexplained—the larger DLPFC gray matter volume at baseline in patients who relapsed and the increases in gray matter volume and

cortical thickness in healthy controls—the study results suggest that neuroimaging techniques may have real-world clinical utility in identifying patients likely to relapse and finding targets for interventions, including neuromodulation, to interrupt the course of recurrent depression.²

¹Zaremba D, Dohm K, Redlich R, Grotegerd D, et al: Association of brain cortical changes with relapse in patients with major depressive disorder. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.0123. From the University of Munster, Germany; and the University of Adelaide, Australia. **Funded by the German Research Foundation; and other sources. Two of 17 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

²Phillips M: A promising future role for neuroimaging in tracking and predicting relapse in major depressive disorder [editorial]. *JAMA Psychiatry* 2018; doi 10.1001/jamapsychiatry.2018.0405. From the University of Pittsburgh, PA. **The author declared no competing interests.**

Creatine Kinase and Aggression

According to the results of a retrospective study, aggression is associated with elevated creatine kinase (CK) levels in patients hospitalized with schizophrenia. Evaluation of CK levels could help identify patients with the potential for aggressive behavior.

Background: CK is an enzyme that is widely used as a biological marker for heart trauma or skeletal muscle damage. It may be increased after physical trauma, intramuscular injections, seizure, neuroleptic malignant syndrome, restraint, and intense exercise. Elevated levels in patients with psychotic mania or schizophrenia could also be related to psychomotor agitation or seclusion.

Methods: Study subjects were nearly 2800 patients consecutively admitted to 5 psychiatric inpatient units of a Chinese university hospital between 2009 and 2013. All patients had a diagnosis of schizophrenia, according to DSM-IV criteria, and had CK measured as part of routine admission blood tests. Before patients received any medication, clinicians documented their aggressive behaviors, including verbal and physical aggression against self or others. Patients were not included in the analysis if they had diseases, injuries, or other events that could increase CK levels.

Results: At admission, 28% of patients had serum CK levels above the normal limits for the assay used (i.e., >226 U/L), and 5.5% of patients were classified as aggressive. Patients aged <30 years and men were overrepresented among both persons with elevated CK and those with aggressive behavior.

Aggression was more common among patients with elevated CK levels, 18% versus 2.6% in patients with CK levels in the normal range (odds ratio,* 8.1). Among patients with aggression, 61% were found to have elevated CK, compared with 16% of non-aggressive patients. A multivariate analysis that excluded CK level found aggressive behavior was also associated with male gender, alcohol abuse, drug abuse, and a history of psychosis. In most patients with elevated CK levels, prevalence of aggression decreased after hospital admission. However, in those with the highest CK levels (i.e., >5 times the upper limit of normal), the prevalence increased.

Discussion: Although the exact relationship between aggression and CK elevation remains unclear, measurement of CK along with evaluation of the other identified risk factors could help predict which patients with schizophrenia will display aggression.

Meng X-D, Cao X, Li T, Li J-P: Creatine kinase (CK) and its association with aggressive behavior in patients with schizophrenia. *Schizophrenia Research* 2018; doi 10.1016/j.schres.2018.02.025. From Sichuan University and Chengdu Medical College, Chengdu City, China. **Funded by the Natural Science Foundation of China. The authors declared no competing interests.**

*See Reference Guide.

Augmented tDCS for Resistant Depression

In a pilot study, transcranial direct current stimulation (tDCS) augmented with a simultaneous cognitive-emotional task had promising results in patients with medication-resistant depression.

Methods: Study subjects were 20 adults with medication-resistant major depressive disorder indicated by a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥ 20 despite adequate antidepressant pharmacotherapy. All participants underwent tDCS with simultaneous Cognitive Emotional Training (CET) 3 times per week for a total of 18 sessions. CET consisted of the Emotional Faces Memory Task, in which patients remembered the emotional expressions of a series of faces on a computer screen. Outcomes were assessed at baseline, mid-treatment, and at treatment end. The primary efficacy measure was change from baseline in MADRS score.

Results: Study participants' depression had not responded to a mean of 1.3 antidepressant drugs in the present episode and 4.7 over the lifetime course of their illness. Of the 20 patients enrolled, 3 did not complete treatment for personal reasons. The mean MADRS score decreased from 30 at baseline to 23 mid-treatment, and further to 18.6 at the end of treatment ($p < 0.001$). Of the 17 patients who completed treatment, 7 (41%) had a $\geq 50\%$ reduction in MADRS score, meeting criteria for treatment response. Patients also reported improvement in psychological symptoms, rumination, and quality of life. For about half of the patients, the duration of brain stimulation was increased from 30 to 40 minutes mid-study to accommodate completion of the CET; results did not differ between patients receiving the 2 tDCS durations. Patients were administered a battery of cognitive tests, but only 1, the Digit Span Total test, showed improvement with treatment. Changes in depression and in measures of cognition were not correlated.

Discussion: Prior studies have found little or no effect of tDCS in patients with medication-resistant depression. Because tDCS is a sub-threshold stimulus, it may be important to add a simultaneous task because ongoing neural activity is necessary to induce lasting neuroplastic changes. CET is hypothesized to activate the dorsolateral prefrontal cortex and the amygdala, regions involved in working memory and emotional recognition. Contrary to the investigators' expectations, CET during tDCS did not enhance cognitive performance.

Martin D, Teng J, Lo T, Alonzo A, et al: Clinical pilot study of transcranial direct current stimulation combined with Cognitive Emotional Training for medication resistant depression. *Journal of Affective Disorders* 2018;232 (May):89–95. From the University of New South Wales, Sydney, Australia; and other institutions. **Funded by the National Alliance for the Research of Schizophrenia and Depression. The authors did not include disclosure of potential conflicts of interest.**

Gene Network Mapping in Schizophrenia

Genome-wide association studies (GWAS) have identified as many as 108 independent loci, containing >300 genes, that are involved in schizophrenia. Antipsychotic drugs bind to numerous proteins, only 2 of which, dopamine and serotonin receptors, have known biological links to schizophrenia. It is highly likely that other, as-yet unidentified pathways are involved in the disease.

Methods: Risk genes for schizophrenia, as with other complex disorders, interact with one another and form a functional network. Researchers at the University of California San Diego mapped a subset of schizophrenia risk genes from the GWAS according to their interactions in order to identify a group of interconnected genes that form the core disease module. They then examined the freely available Drug-Gene Interaction database and identified 88 of these genes that were targeted by ≥ 1 of 64 antipsychotic drugs to identify interactions among drug targets and risk genes.

Results: Antipsychotic drug targets or their nearest neighboring genes were statistically associated with schizophrenia, and these connected genes tended to be involved in developmental biology, learning or memory, and cognition. Four genes were both a risk gene and a drug target gene: glutamate metabotropic receptor 3, dopamine receptor D2, cholinergic muscarinic receptor 4, and CYP2D6. Many other risk genes overlapped or connected with genes that were antipsychotic drug targets.

The investigators also identified risk genes that were not connected to antipsychotic targets as potentially druggable targets. Multiple gene clusters with potential as targets for cognitive enhancers were found, and 11 drugs approved for other indications and 8 experimental drugs were identified that could potentially target schizophrenia genes. Interestingly, 1 group of genes—nicotinic acetylcholine receptor genes—is thought to be important in the cognitive deficits of schizophrenia and also in Alzheimer’s disease. These genes are targeted by several existing drugs, including galantamine (*Razadyne*), that are currently being investigated as cognitive enhancers in schizophrenia.

Discussion: The present results indicate an overlap exists between the pathological mechanisms of schizophrenia and the pharmacological mechanisms of antipsychotics. Information regarding this overlap could be used to advance the development of more efficient multitarget drugs directed at poorly treated aspects of schizophrenia.

Kauppi K, Rosenthal S, Lo M-T, Sanyal N, et al: Revisiting antipsychotic drug actions through gene networks associated with schizophrenia. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2017.17040410. From the University of California San Diego; and other institutions. **Funded by the NIMH. Two of 9 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

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