

Cognitive Dysfunction in Psychiatric Illness: A Neglected Domain

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Cognitive disturbances are an integral part of bipolar disorders. In this issue of *The Journal*, Burdick et al¹ review the studies of cognitive dysfunction in bipolar disorder and address the challenges involved in the design of trials to treat neurocognition in bipolar disorder. The authors rightly identify heterogeneity of illness manifestation and course, comorbid psychiatric illness, and polypharmacy as 3 of the major challenges. They also make practical recommendations to deal with these challenges in study design.

This article is a welcome addition to the literature in that it addresses the neglect of cognitive dysfunction research in psychiatric patients. One important reason for this is the lack of efficacious therapies for this symptom domain (including some notable failures of new pharmacotherapies in schizophrenia to treat cognitive dysfunction²⁻⁷) leading to lack of research funding from both pharmaceutical companies and nonpharmaceutical sources. The heterogeneity of DSM-diagnosed patients along with lack of control for variables contributing to cognitive dysfunction prior to randomization may be one of the contributing factors to these negative trials. Recently, the National Institute of Mental Health with the Research Domain Criteria (RDoC) initiative has made cognitive functioning one of the key constructs in the dimensional approach to diagnosis.⁸ Even though several variables including sociodemographic, clinical, environmental, neurocognitive, and pharmacologic affect functional outcomes in psychiatric patients,⁹ most clinicians do not appreciate that cognitive dysfunction is perhaps the most important domain predicting prognosis in patients with a wide variety of psychiatric illnesses, including bipolar disorders, dementia, schizophrenia, major depressive disorder (MDD), autism, attention-deficit/hyperactivity disorder (ADHD), and others. Even though the dementia field has been familiar with cognitive dysfunction, the fields of schizophrenia, mood disorders (particularly MDD), ADHD, and autism have been latecomers to the arena. Since young people are most affected by these illnesses and accompanying cognitive deficits, strategies to prevent their occurrence, change their course, or treat them by focusing on novel targets at a molecular level is of paramount importance to improve outcomes.

Bipolar disorder offers an example that illustrates some of the challenges in addressing cognitive deficits. Even

though, as the authors point out, cognitive disturbances are more common in bipolar I versus II disorder and psychotic versus nonpsychotic patients, the more important question is whether there are any differences in the outcome and response to treatments (both pharmacotherapies and nonpharmacotherapies) of patients who have bipolar disorder with similar cognitive dysfunction, irrespective of whether they have bipolar I or II disorder, psychosis or not, comorbid anxiety disorders or not.

Also, since the source of cognitive dysfunction in bipolar patients can be primary (ie, neurodevelopmental aberration, obstetric complications, allostatic load) or secondary (ie, depressive symptoms, medication side effects or comorbid illness), the interventions may be differentially effective in these subpopulations. Likewise, bipolar patients are unique in demonstrating affective polarity during their clinical course completely different from patients with other psychiatric disorders. We may expect differential manifestations of cognitive decline or impairment in specific cognitive domains in bipolar patients. Therefore, such issues should be also addressed and incorporated in clinical trial design. Another point should be whether a similar cognitive battery should be utilized in both acute and maintenance clinical trials for bipolar patients, since the study objectives and clinical status of subjects would be different in some aspects. For example, acutely ill bipolar patients may have more confounding clinical factors as well may be on a different regimen of medications compared with those in the maintenance treatment phase.

The time course of cognitive impairment in bipolar disorder is not well studied. Some functions appear to be associated with clinical improvement, including measures of executive function and verbal fluency.¹⁰ Other deficits have been shown to be more persistent, though it is unclear if cognitive improvement simply lags behind affective instability. Hence, it is also crucial to address such issues in designing clinical trials in bipolar patients.

Even though the authors addressed psychiatric comorbidity including substance abuse and ADHD as a challenge to research design, we should not neglect other medical illnesses (eg, obesity), which are rampant in bipolar patients. For instance, they can affect cognitive function of bipolar patients adversely and thereby disturb proper assessment of cognition, potentially leading to noise in clinical trial results.

Medications may be helpful in alleviating mood symptoms and preventing relapse of symptoms but may not do much to improve psychosocial functioning and cognitive deficits. Some of the seminal work by Dr Vieta's group at the University

Submitted: January 7, 2015; accepted January 9, 2015.

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J Clin Psychiatry 2015;76(3):e375-e377 (doi:10.4088/JCP.15com09780).

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of Barcelona has shown that functional remediation involving 21 weekly sessions, each of them 90 minutes in duration (targeting both cognition and psychosocial issues), can improve functional outcomes in patients with bipolar disorder despite optimal pharmacotherapy. The largest effect sizes were seen in the cognitive domains, particularly verbal memory.¹¹⁻¹³ However, the rates of response in these studies may be enhanced by choosing populations more responsive to functional remediation based on baseline cognitive dysfunction and variables contributing to it, as discussed above. Tailored treatments in bipolar disorder may yield more bang for the buck rather than the shotgun approach psychiatry has embraced.

Another common yet devastating illness for which existing pharmacotherapies have limitations possibly due to their negligible effects on cognitive deficits is MDD. In the STAR*D trial,¹⁴ even after 4 levels of treatment, approximately 30% of patients had not achieved symptomatic remission, let alone functional remission. In the real world, a very small minority of patients receive the levels of treatment that STAR*D participants received, arguing for even worse outcomes.

Research on treating cognitive dysfunction in MDD has lagged far behind schizophrenia and bipolar disorders, even though it is a far more common illness with greater costs to society. Even though “hot cognition” (negative emotional bias) responds to all antidepressant treatments, “cold cognition” (attention, executive dysfunction, processing speed, memory, etc) does not. In a recent issue of *The Journal*, Keefe et al¹⁵ reviewed the literature (a total of 43 studies met criteria) on treating cold cognition in MDD either with monotherapy or adjunctive therapy and found negligible effects with monotherapy (only verbal memory improved, with an effect size of 0.1) and modest effects with adjunctive therapy (effects sizes of 0.1–0.4). Most recently, there have been promising data with vortioxetine a new antidepressant with actions affecting multiple serotonin receptors for treating cognitive disturbances in MDD. Vortioxetine demonstrated efficacy in 3 double-blind placebo controlled-trials,¹⁶⁻¹⁸ including 2^{16,17} where it showed superiority to duloxetine in improving a broader spectrum of cognitive disturbances, including cold cognition. This finding may argue for tailored pharmacotherapy for patients with predominant cognitive dysfunction with vortioxetine.

Cognitive impairment is a core feature of schizophrenia. It starts in the premorbid phase (as early as first grade) and continues throughout the course of illness. Patients with schizophrenia score 1.5–2.5 standard deviations lower than healthy controls on composite cognitive scores. Recent research shows that the antipsychotics, including second-generation antipsychotics, are minimally efficacious in treating this symptom domain. Superior efficacy for second-generation antipsychotics may be explained by practice effects, study design, or inappropriate dose comparisons.¹⁹ Working memory and social cognition may be spared early in the illness.²⁰ Trials of adjuncts to treat cognitive deficits in schizophrenia have been disappointing to say the least.^{2-7,21}

Ongoing late-stage trials with novel agents like encenicline ($\alpha 7$ nicotinic acetylcholine receptor partial agonist) continue to hopefully fulfill this unmet need.

The development of self-rating scales of cognitive function specifically designed for bipolar patients may also enhance the understanding and management of cognitive deficits in bipolar patients. Traditional cognitive assessment packages are time, cost, and effort consuming, leading to the neglect of regular monitoring of the changes in cognitive function in bipolar patients. With wide utilization of brief self-rating scales for bipolar patients, we may more easily track the natural course of cognitive function in bipolar patients, as a result of which more deliberated cognitive assessment batteries can be designed. This may also help clinicians and patients find clinical predictors correlated with cognitive changes in clinical practice.

Cognitive deficits are an integral part of most of the common psychiatric illnesses and predict a poor prognosis. There is a great unmet need to treat this symptom domain in order to achieve not just symptomatic remission but functional remission in patients with bipolar disorder. Addressing the methodological issues and study trial design is an important first step to achieve this outcome.

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Potential conflicts of interest: Dr Masand has been a consultant for Forest, Actavis, Lundbeck, Merck, Pamlab, Pfizer, Sunovion, and Takeda; has served on speaker's bureau from Actavis, Forest, GlaxoSmithKline, Lundbeck, Merck, Pamlab, Pfizer, Sunovion, and Takeda; and has stock ownership in and is an employee of Global Medical Education. Dr Pae has no conflict of interest.

Funding/support: None reported.

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