Cognitive Deficits in Bipolar Individuals: Implications for Clinical Practice

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Kraepelin's classic description of manic depressive illness, based on longitudinal observations of clinical history and symptomatic patterns, included as a core feature, the belief that there was an episodic pattern of illness alternating with periods of resumption of normal function. However, more recent research calls this view into question. Increasingly, we are learning that cognitive deficits in individuals with bipolar disorder involve attention, executive function, verbal fluency, and memory [1]. Other studies have also indicated that remitted individuals with bipolar disorder experience significant cognitive impairment [2,3]. After performing an impressive *meta*-analysis of recent studies comparing the full-scale intelligence quotient (IQ) scores [WAIS-R], of bipolar patients and healthy volunteers, Goodwin and Jamison [4] report that remitted bipolar individuals compared to healthy controls had deficits in verbal and performance IQ, psychomotor functioning, cognitive and motor speed, attention, learning and memory, and executive function. Furthermore, their *meta*-analysis showed that remitted samples generally had the same level of deficits as acutely ill groups in cognitive areas such as memory and learning. They hypothesize that attentional disruption may instigate the more widespread pattern of generalized cognitive impairment. Additionally, Zarate and colleagues [5] have argued that the persistent neuropsychological deficits found in bipolar subjects may be associated with functional impairment. Some have estimated that 30–60% of individuals with bipolar disorder fail to regain full functioning in occupational and so-

cial domains after achieving a remission of mood symptoms [6]. Other factors that may influence the presentation of cognitive deficits in a given individual include subsyndromal mood symptoms, comorbid disorders (i.e., substance use), or other iatrogenic factors (i.e., medications). The effect of current treatments on cognitive deficits in individuals with bipolar disorder adds an additional level of complexity to considerations of benefit relative to harm associated with our current treatments. In most studies of bipolar individuals in a remitted state, the subjects are maintained on medications that may have considerable adverse effects on cognition. Medications, such as lithium, the anticonvulsant medications, benzodiazepines, and/or the antipsychotic medications are mainstays of treatment for bipolar disorder and most patients are on a combination of several medications. For example, in the large NIMH-sponsored STEP-BD study, subjects were on average taking more than four medications daily. Thus, the cognitive deficits found in individuals with bipolar disorder who achieve remission, may well be compounded by adverse effects of the commonly used medications as well as consequences of the disease process. Nonetheless, it is reasonable to conclude that cognitive deficits in bipolar individuals may contribute significantly to functional impairment and may contribute to considerable social and economic burden to the individual.

In this issue, Iosifescu and colleagues [7] present very interesting and important data on a treatment for cognitive dysfunction in individuals with bipolar disorder.

They report on nineteen euthymic bipolar individuals compared to 10 age-and-gender-matched healthy volunteers, who underwent cognitive testing before and after open-label treatment with galantamine-ER. Galantamine-ER is an anticholinesterase inhibitor that is indicated for the treatment of mild-to-moderate dementia. Additionally, study subjects underwent proton magnetic resonance spectroscopy measurement of hippocampal N-acetyl aspartate and choline containing compounds before and after medication treatment, whereas healthy volunteers were examined only at baseline. They found that compared to the healthy volunteers, bipolar subjects had higher baseline subjective cognitive deficits and lower scores on measures of attention, and verbal episodic memory. Additionally, in the left hippocampus, NAA and choline decreased in bipolar subjects during treatment. The authors found that bipolar subjects with cognitive dysfunction at baseline had significant improvement in subjective cognitive scores and on objective tests of attention and verbal memory with galantamine-ER treatment. Furthermore, this improved cognition was associated with increases in neuronal viability, and normalization of lipid membrane metabolism in the left hippocampus.

Despite the relatively low number of subjects in this cohort, it is the largest study published to date on the treatment of cognitive function in subjects with bipolar disorder. This alone illustrates the lack of attention to this widespread problem. More importantly, these euthymic subjects experienced significant improvement with this treatment. Iosifescu et al. argue that neither subsyndromal mood symptoms nor substance comorbidity played a contribution toward the cognitive deficits of their subjects. The fact that these individuals experienced benefit while on their other medications is also very encouraging and suggests cognitive enhancing medication treatments could complement our current treatments and help the clinician to create a personalized treatment for an individual that includes effective treatment of residual cognitive deficits, and promotes better functional capacity.

A very exciting aspect of this report is the authors' examination of proton magnetic resonance spectroscopy (1H-MRS) data from subjects' pre- and post-galantamine-ER treatment. Although only eight subjects constituted this analyzable population, there was a normalization of measures of left and right hippocampal n-acetyl aspartate and choline containing compounds, measures suggests increased neuronal viability and increased membrane lipid metabolism and membrane turn-over. The authors state that these neuronal-biological correlates of normalization of lipid membrane metabolism in the hippocampus, demonstrate a neuroprotective effect

of the treatment. This examination of neuropsychological measures of galantamine-ER's improvement of baseline cognitive deficits and the spectroscopy data indicating normalization of neuronal viability and neuronal revitalization present a sophisticated model for psychiatric researchers to emulate. The authors demonstrate how to translate and incorporate basic science data, in this case derived from spectroscopic studies, into a clinical trial therein offering a pathophysiological explanation for the results. This kind of study is in the spirit of the NIMH Strategic Plan [8] to promote translational and clinical research to understand the genetic, neurobiological, behavioral, environmental, and experiential factors that contribute to mental disorders; and to develop treatments that can be personalized to improve outcomes for individuals with mental illnesses. Effective treatment of cognitive deficits, in remitted bipolar individuals, can benefit an individual on personal, interpersonal, and functional levels. To be able to successfully monitor and treat, for example, the metabolomic, neuropsychological, functional, genetic and cognitive problems of our patients, hints of a possible model of clinical practice of the future.

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