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Cognitive functioning in bipolar and co-occurring substance use disorders: a missing piece in the puzzle

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The co-occurrence of bipolar and substance use disorders (SUD) poses one of the most difficult challenges to psychiatric care. Acute mania complicated by SUD is characterized by less favorable remission and manic symptoms of greater severity, including more extreme forms of mood lability, impulsive actions, and violence (1). In addition, bipolar disorder patients with co-occurring SUD typically present with a much more severe and chronic course of illness. Their first manic episode typically occurs at an earlier age, and patients with this combination of disorders tend to suffer from greater psychosocial disability, more limited long-term recovery, and higher mortality rates (2). A growing recognition of these problems has led to pioneering advances in the development of both pharmacological and psychosocial interventions that are specifically designed to address the needs of these vulnerable patients (3). However, at this point, the course of this condition often remains refractory in nature, awaiting conceptual and clinical breakthrough.

A possible avenue for theoretical and clinical advancement may emerge from examining the potential role that neurocognitive impairment plays in exacerbating the illness severity of dually diagnosed bipolar disorder patients. In recent years, a growing volume of research on the neuropsychology of bipolar disorder has generated challenging evidence to Kraepelin's inveterate notion that this illness typically reaches a state of full remission. The weight of the evidence indicates the presence of debilitating cognitive impairment, persisting well into periods of euthymia, especially in patients who suffer from multiple mood episodes (4). Similarly, SUD in general, and alcohol dependence in particular, are associated with clinically significant neuropsychological deficits that may fail to fully remit even after prolonged abstinence (5).

Although the neuropsychology of both bipolar disorder and SUD has been studied extensively, this comorbid condition has largely been ignored. With few exceptions, most studies to date systematically excluded dually diagnosed patients for methodological reasons, so little is known about the cognitive functioning of this group. One preliminary study has documented greater cognitive decrements in euthymic bipolar disorder outpatients with a history of alcohol dependence (6). A similar finding emerged in a more recent study from our group, which examined the cognitive functioning of inpatients upon discharge

from the hospital (7). In this study, bipolar disorder patients with co-occurring alcohol dependence exhibited more severe impairment in executive functioning relative to patients with bipolar disorder without SUD. Patients meeting DSM-IV diagnostic criteria for alcohol dependence during the 6 months prior to admission also displayed more significant impairment on measures of verbal and nonverbal memory. These results are consistent with the hypothesis that neuropsychological deficits associated with both bipolar disorder and alcohol dependence combine to produce impairment of greater severity in dually diagnosed patients. However, in light of the paucity of extant data, the nature and significance of the neuropsychological impairment in this patient population remains largely unanswered at this point. In a broader view, the more central question of whether SUD adds a functionally debilitating cognitive impairment to the deficits inherent in bipolar disorder has not yet been addressed.

A cognitive formulation adds a plausible account for the refractory nature of dually diagnosed bipolar disorder patients, especially in cases where alcohol dependence is of primary concern. The severity of cognitive impairment predicts treatment outcome in bipolar disorder (8) and likelihood of remission in alcohol dependence (9). In particular, severe deficits in executive functioning, the cognitive domain implicated most consistently across studies in both disorders (10,11) can further erode already compromised mechanisms of impulse control necessary for maintaining sobriety. Uncontrolled alcohol use can in turn exacerbate the mood disturbance via chronic stress, impaired functioning, and other factors. Even during times of abstinence, severe executive dysfunction can be detrimental to patients' ability to remain euthymic. Specifically, significant deficits in attention, organization, and planning can seriously compromise the ability to adhere to pharmacological interventions or access psychosocial treatment and additional supportive services. Thus, although the data for elucidating the mechanism that exacerbates the illness severity of dually diagnosed bipolar disorder patients are not yet available, it may be plausible to hypothesize that the chronic instability or limited long-term recovery observed in these patients may at least partly result from severe executive and related cognitive impairment.

More severe cognitive impairment may also explain why dually diagnosed bipolar disorder patients suffer from greater psychosocial disability. Even in euthymic patients without SUD, neurological abnormalities indicative of frontal lobe and executive dysfunction predict social disability (8). More specifically, deficits in planning and problem-solving can seriously compromise the ability of patients to cope with everyday life and negotiate the demands of work and family. Psychosocial functioning, in fact, was found to correlate more with neuropsychological measures than with other clinical variables of bipolar disorder (4). This suggests that cognitive functioning in patients with bipolar disorder may play an important mediating role between illness process and functional outcome. It is therefore possible that bipolar disorder patients with co-occurring SUD suffer greater psychosocial disability particularly due to more severe cognitive impairment.

Several plausible mechanisms may account for the hypothesized synergy of cognitive impairment in bipolar disorder with co-occurring SUD. First, chronic substance exposure may have direct neurotoxic effects on the brain, which manifest in the exacerbation of existing cognitive deficits. Alternatively, mood episodes of greater severity and duration may lead to greater cognitive impairment. The severity of mood disturbance has been independently associated with both poor cognitive functioning and the co-occurrence of SUD. Dually diagnosed patients may therefore happen to suffer from a more severe form of bipolar disorder, whereby chronic mood instability exacerbates neuro-degeneration and cognitive decline (6). Conversely, it is also possible that the presence of greater cognitive impairment prior to the first manic episode leads to a more severe course of illness.

According to this line of reasoning, cognitive disability may pose stressful functional limitations that contribute to both mood instability and substance dependence. Elucidating the potential role cognitive impairment plays in the etiology of bipolar disorder with co-occurring SUD requires a comprehensive investigation. During its preliminary stage, the investigation may seek to substantiate previous findings through large-scale replications. In this critical phase, it may be useful to distinguish among dependence upon different substances, as there may be some variability in the cognitive effects of different substances of abuse. Heeding pragmatic considerations, the investigation may maintain its initial focus on the co-occurrence of alcohol dependence. As the neuro-cognitive effects of alcohol have been studied most extensively, cognitive data related to the co-occurrence of alcohol dependence may be easier to interpret than comparable data that are associated with the co-occurrence of other substances.

Moving forward, prospective studies may attempt to document the degree of fluctuation in the level of cognitive impairment dually diagnosed patients experience over the course of illness. Whereas the general trend is expected to reflect a process of cognitive decline, patients may experience some recovery of cognitive functions over the course of remission from an acute episode. In alcohol dependence, prolonged abstinence leads to a clear, albeit partial, neurological and cognitive recovery (11). A similar pattern may emerge in bipolar disorder with respect to the abatement of residual mood symptoms as patients recover from acute manic or depressive episodes. The question of cognitive recovery is conceptually important, as it is relevant for understanding the course of illness and patients' needs. In this respect, understanding the level of cognitive impairment patients experience at the time of discharge from inpatient care and the extent of cognitive recovery that occurs with affective remission thereafter may help to design outpatient interventions and accommodations that better facilitate recovery.

The investigation of cognitive functioning in dually diagnosed bipolar disorder patients must also include brain-based research. Research in bipolar disorder provides consistent evidence for abnormal activity of the hypothalamic-pituitary-adrenal (HPA) axis across manic (12), depressed (13), mixed (14), and euthymic (15) phases, and there is some speculation that this abnormality may be accompanied by neurotoxic effects (16). A large volume of studies of alcohol dependence have also identified abnormal HPA functioning that may be related to other forms of substance use disorder and suicidal behavior (17,18,19). Since both bipolar disorder and alcohol dependence are associated with HPA dysregulation, it may be informative to investigate HPA functioning in dually diagnosed patients and explore possible links to brain and cognitive functioning.

Neuro-imaging studies may carry a substantial contribution to the proposed investigation. Although the neurophysiological etiology of bipolar disorder is not entirely clear, studies suggest a number of premorbid structural and functional abnormalities in the prefrontal cortex and subcortical regions (20). These neurological aberrations may be important for understanding enduring executive impairment in chronic patients (21). Research on the neurobiology of alcohol dependence also implicates brain regions that are important for executive functioning. For example, chronic alcohol exposure causes structural changes, including general loss of gray and white matter volume and a specific increase in neuroatrophy in the frontal cortex (11). Longitudinal neuroimaging studies can help to explore whether dually diagnosed bipolar disorder patients suffer from a synergistic neurological impairment that increases executive dysfunction.

Understanding the severity of cognitive impairment in dually diagnosed bipolar disorder patients may carry important implications for illness management, especially at the time of discharge from inpatient care. Cognitive disability is likely to emerge more acutely during

an inpatient admission due to the temporal proximity to the peak of both mood disturbance and substance use. Therefore, a routine assessment of cognitive status at the time of discharge can help to determine the level of support the patients need in the post-discharge environment. A 3-month follow up may help to monitor cognitive recovery and guide patients with decisions about work and balancing additional demands. Repeated neuropsychological assessment can also assist with forming more effective long-term plans with respect to the degree of structure, accommodations, and supervision that patients require for maintaining stability on an outpatient basis. Overall, neuropsychological monitoring may help in guiding patient care in a manner that reduces stress and potentially decreases readmissions.

Understanding the cognitive status of patients is also important for treatment. As already recognized in the treatment of alcohol dependence, cognitive impairment may hamper the ability to benefit from psychotherapy (22). Deficits in memory, attention and organization limit patients' ability to absorb and process information in a manner that prevents effective engagement in therapy. Several studies have indicated that neuropsychological status is associated with treatment outcome in alcohol dependence, in which pronounced deficits limit the ability of patients to learn what was presented during the sessions (23, 24). Research has also demonstrated that some cognitive deficits that do not remit spontaneously with continued abstinence improve with remediation via cognitive stimulation (25), and that the recovery of function enhances performance across a wide variety of tasks that are only distantly related in content to the training procedure (23). There is also some evidence that cognitive stimulation can enhance the acquisition of definable components of alcohol dependence treatment (25). The potential cognitive vulnerability of dually diagnosed bipolar disorder patients may render cognitive remediation procedures particularly relevant for enhancing their treatment outcome.

It is also important to recognize that cognitive impairment can compromise treatment outcome indirectly. Pronounced deficits in organizational skills and planning can make even basic tasks such as adhering to medication and keeping therapy appointments quite challenging. To cope with these challenges, treatment may need to integrate skill building that is designed to compensate for cognitive impairment. Applying behavioral strategies that enhance organization and aid recall can increase overall level of functioning and the ability to benefit from treatment.

Given the potential elevation in risk for cognitive disability, pharmacological treatment of dually diagnosed bipolar disorder patients may need to be particularly sensitive to cognitive side effects. Further compromise of cognitive functioning of impaired patients may exacerbate the degree of psychosocial disability and result in a devastating loss of quality of life. Although some controversy emerged around the cognitive side effects of lithium and neuroleptics, there is agreement that anticholinergic agents can be detrimental to learning and memory (26). Reported cognitive side effects of anticonvulsant medication tend to be mild (27). A recent study presented preliminary data indicating that lamotrigine may have a safer neurocognitive profile in bipolar patients relative to other anticonvulsants (28). Looking forward, as pharmacological research continues to develop, it may be important to identify effective agents with fewer cognitive side effects for the treatment of dually diagnosed bipolar disorder patients. In addition, the pharmacological development of agents that can alleviate their cognitive deficits more directly may also be warranted.

To conclude, among all psychiatric conditions, bipolar disorder with co-occurring SUD is one of the most refractory and difficult to manage (29). Given that both disorders are marked by significant brain abnormalities and debilitating cognitive impairment, it is possible that these deficits converge with a detrimental additive effect in patients who suffer

from this dual diagnosis. A cognitive formulation of dually diagnosed bipolar disorder patients can help in explaining why they suffer from a more severe progression of illness and level of psychosocial disability. As extant data are scant and narrow in scope, this hypothesis remains speculative at this point. However, it does offer a potentially fruitful avenue for research development. Pending empirical support, a cognitive formulation of dually diagnosed bipolar disorder patients may foster new prevention strategies, clinical insights, and interventions that will ultimately reduce suffering and cost.

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