Risk for cognitive impairment among HIV-infected persons with bipolar disorder

Clinicians and clinical neuroscientists are aware that individuals with bipolar disorder are at greater risk for developing serious medical, psychiatric, and substance-use comorbidities as compared with the general population.\textsuperscript{1,2} Less widely appreciated, however, is the observation that HIV infection appears to be more prevalent among persons with bipolar disorder and that both conditions pose significant risk for cognitive impairment.\textsuperscript{3} Higher rates of HIV infection among persons with bipolar disorder should not be surprising, given that infection and transmission of HIV involves risk factors that converge with bipolar disorder (eg, impulsivity, substance abuse). These factors likely also worsen adherence to treatment for both bipolar and HIV illness, and may adversely impact health-related quality of life and therapeutic outcomes. The public health consequence may be that nonadherence to antiretroviral therapy could lead to higher rates of transmission of treatment-resistant strains of HIV that can evolve with sporadic adherence. The intersection of bipolar disorder and HIV therefore merits discussion by clinicians, researchers, and policy makers.

If mental health clinicians adopt the recent Centers for Disease Control recommendation that all persons in clinical care be tested for HIV, we might expect that more HIV-infected persons with bipolar disorder will be identified who had not previously been diagnosed or treated for existing HIV infection.\textsuperscript{4} When addressing the complex combination of HIV infection, substance abuse or dependence, and bipolar disorder, it is important to recognize that each of these factors may be associated with substantial cognitive deficits. These neurocognitive impairments may impact on the ability to function in social and occupational settings, to follow through with treatment recommendations, and to manage their demanding medical conditions. Below we review the evidence for neuropsychological (NP) impairment among persons with bipolar disorder, HIV infection, and substance dependence (ie, methamphetamine dependence) as independent disorders. Our hypothesis, and the basis for our ongoing research, is that the presence of significant medical comorbidities (eg, HIV infection) and substance use (eg, methamphetamine dependence) may further compound the risk for additive neurocognitive impairments among persons with bipolar disorder. We describe our new program of research in bipolar disorder and comorbid HIV, and present data showing elevated rates of methamphetamine dependence among persons with bipolar disorder. Finally, we discuss how cognitive impairment may be a significant predictor of everyday functioning difficulties (eg, medication nonadherence).

**Neuropsychological impairment among persons with bipolar disorder**

Recent studies of individuals with bipolar disorder suggest that NP impairment is prevalent, and intermediate in severity between patients with schizophrenia and healthy comparison participants.\textsuperscript{5,6} NP impairments, particularly deficits in attention, processing speed, episodic memory, and executive functions (eg, set-shifting, complex problem-solving), are thought to persist during euthymic states between episodes (Table I).\textsuperscript{9-14}

**Neuropsychological impairment among persons with HIV infection**

HIV infection is characterized by an acute, often febrile, phase lasting days or weeks, a prolonged medically
asymptomatic period, and a symptomatic phase of multisystem disease caused by immunosuppression. HIV is also known to cause neuropsychological (NP) impairments, particularly in the areas of attention/working memory, motor coordination, processing speed, learning, and attention (Table I).\textsuperscript{15,16} NP impairment tends to worsen with disease severity, with the greatest NP impairments observed among individuals with AIDS.\textsuperscript{16} HIV enters the central nervous system soon after infection, and mild cognitive impairment has been observed in approximately 30% of medically asymptomatic HIV-infected patients, whereas some form of NP impairment is observed in over 50% of individuals in later-stage HIV disease.\textsuperscript{15} Although antiretroviral treatments have greatly improved the longevity and quality of life for persons living with HIV infection, the prevalence of HIV-associated neurocognitive disorders (HAND) has not declined.\textsuperscript{17}

**Neuropsychological impairment among methamphetamine users**

Persons with bipolar disorder and individuals with HIV are at increased risk for both alcohol and other substance abuse and dependence.\textsuperscript{2,18} The NP impairments associated with various drugs of abuse differ; however, most illicit substances and alcohol, when used in significant quantities or over a substantial period of time, are likely to produce measurable neuropsychological deficits that may persist for extended periods, even after abstinence is achieved. Here, we focus on the neuropsychological difficulties associated with methamphetamine use disorders because: (i) its use is on the rise in the United States\textsuperscript{16}; (ii) cognitive impairments are common and substantial among abusers; and (iii) it is the most frequently abused substance, aside from marijuana and alcohol, worldwide.\textsuperscript{20} A recent review and meta-analysis showed that methamphetamine abuse or dependence resulted in neuropsychological impairments of medium effect size in the domains of episodic memory, executive functioning, information processing speed, motor skills, language, and visuoconstructive abilities.\textsuperscript{21} The cognitive domains with the largest effect sizes are listed in Table I. Furthermore, evidence suggests that when methamphetamine abuse or dependence is combined with HIV infection, there is additive neuropsychological impairment.\textsuperscript{22,23}

| Bipolar disorder | HIV | Methamphetamine |
|------------------|-----|-----------------|
| Learning/memory  | Learning | Learning/memory |
| Processing speed | Processing speed | Processing speed |
| Attention/working memory | Attention/working memory | Executive functions |
| Executive Functions | Motor skills | |

Table I. Overlap in neuropsychological domains commonly impaired among bipolar disorder, HIV infection, and methamphetamine abuse/dependence.
group without bipolar disorder met criteria for a lifetime diagnosis of Major Depressive Disorder (MDD); however, only 11% (2/18) met criteria for a current depressive episode. Twenty-seven percent (4/15) of participants in the bipolar group met criteria for a current depressive episode and an equivalent amount (27%; 4/15) met criteria for a current manic episode (2 manic episodes, 1 hypomanic episode, 1 extreme irritability episode). Also as anticipated, participants in the bipolar group tended to take a greater number of psychotropic medications; 93% (14/15) in bipolar group were taking more than one psychotropic medication as compared with 33% (6/18) in the group without bipolar disorder. The bipolar group also had higher scores on both the Young Mania Rating Scale and the Beck Depression Inventory-II, and lower scores on global assessment of functioning.

The rates of current alcohol, marijuana, and methamphetamine dependence were relatively low in both groups; however, rates of lifetime marijuana and methamphetamine dependence were elevated among participants with bipolar disorder and HIV infection as compared with those with HIV alone, and rates of lifetime alcohol dependence were elevated in both groups (Table II). When examining alcohol or dependence of methamphetamine instead of focusing exclusively on dependence, 65% (9/15) of the bipolar group met criteria for lifetime methamphetamine abuse or dependence as compared with 28% (5/18) in the group without bipolar disorder.

Detailed neuropsychological test results are pending larger sample sizes; however, with the cognitive impairments found in both bipolar disorder and persons with methamphetamine dependence, we anticipate significant neuropsychological impairments among our participants with both bipolar disorder and HIV infection, and possibly even greater impairments among those with bipolar disorder, HIV infection, and methamphetamine dependence.

**Implications of impaired cognition for everyday functioning among persons with bipolar disorder**

Cognitive impairment appears to be one of the strongest predictors of everyday functioning difficulties in several populations including bipolar disorder and HIV infection. Medication adherence, an extremely important daily activity for persons with significant medical or psychiatric problems, appears to be consistently related to cognitive abilities among individuals with HIV infection and persons with bipolar disorder.

Specific deficits in the NP domains of executive functioning, attention, and memory have been shown to be associated with poor medication adherence. Therefore, the convergence of risk for cognitive impairment among persons with comorbid HIV, BD, and methamphetamine abuse or dependence may make persons with these multiple risk factors particularly susceptible to nonadherence and other everyday functioning difficulties (Figure 1).
Summary

Persons with bipolar disorder are at risk for medical and psychiatric comorbidities, including those known to independently cause neuropsychological impairment (e.g., HIV infection, methamphetamine dependence). We suggest that these conditions may confer additional risk for the development of neuropsychological impairment among persons with bipolar disorder. We speculate that cognitive difficulties in bipolar HIV+ patients may impact medication adherence and other everyday functioning tasks. Poor adherence to psychotropics may lead to mood destabilization, whereas inconsistent adherence to antiretroviral medications may lead to the development of treatment-resistant strains of HIV. Substance abuse may further destabilize the care of these individuals and may additionally contribute to cognitive impairments.

Additional research is needed to better understand the neuropsychological abilities of patients with bipolar disorder and other serious comorbidities, including the extent of impairment, its features, likelihood for progression, relationship to HIV exposure, and impact on everyday functioning abilities among the multiply affected. The exact relationship between bipolar disorder and methamphetamine abuse and dependence also warrants further investigation. Finally, targeted interventions for complex cases at risk for neuropsychological impairment are needed (see Depp et al in this issue, p 239); improving medication adherence seems to be one area for intervention that is important and attainable.

This work was supported by the National Institute of Mental Health (R03 MH078785 and P30 MH 62512) and the California HIV/AIDS Research Program IDEA Award (ID06-SD-201).

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Figure 1. Bipolar disorder, HIV, and substance abuse may lead to neuropsychological impairments that may impact everyday functioning activities such as medication adherence. Medication nonadherence may then in turn exacerbate both HIV and bipolar disorder.
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