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Predictors of psychotropic medication adherence among HIV+ individuals living with bipolar disorder

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Abstract

Objective—HIV infection and bipolar disorder (HIV/BD) are highly comorbid and associated with frontostriatal disruption, emotional dysregulation and neurocognitive impairment. Psychiatric and cognitive factors have been linked to antiretroviral nonadherence; however, predictors of psychotropic adherence among HIV+ individuals with psychiatric comorbidities have not been explored. We evaluated predictors of psychotropic adherence among HIV/BD individuals.

Method—Psychiatric medication adherence of 50 HIV/BD participants was tracked for 30-days using Medication Event Monitoring Systems (MEMS). Participants completed neurocognitive, neuromedical, and psychiatric batteries.

Results—Mean psychotropic adherence rate was 78%; 56% of participants achieved 90% adherence. Younger age and onset of depressive symptoms, more severe current depressive symptoms, number of previous psychiatric hospitalizations and suicide attempts, poorer neurocognition, and more negative attitudes and self-beliefs toward medications univariably predicted worse psychotropic adherence ($p < .10$). A multivariable model demonstrated a combination of current depressive symptoms and more negative attitudes toward medications significantly predicting poorer adherence ($R^2 = 0.27$, $p < 0.003$). Secondary analyses revealed an interaction between neurocognition and mood, such that HIV/BD with greater executive dysfunction and depressive symptoms evidenced the poorest psychotropic adherence ($p < 0.001$).

Conclusions—Both psychiatric and neurocognitive factors contribute to poorer psychotropic adherence among HIV+ individuals with serious mental illness. Adherence interventions aimed at remediating these factors may be especially fruitful.

Keywords

Comorbidity; Depression; Cognition; Attitude

Introduction

Bipolar disorder (BD) and HIV infection demonstrate disproportionately high comorbidity rates contributing to the complex clinical presentation and treatment of these populations. In persons with BD, approximately 10% are also infected with HIV, and among those with HIV infection, between 2.6 to 9.1% also have BD [1,2]. The concurrent neural burden of these two conditions preferentially disrupts the frontostriatal systems [3,4] and, as such, HIV/BD individuals are at a greater risk for both neurocognitive impairment [5] and emotional dysregulation [6]. Downstream, given that neurocognitive and mood disruption are associated with poorer medication adherence in singly affected populations, it is not surprising that emerging evidence suggests those with co-occurring HIV and BD demonstrate an even greater increased risk for medication nonadherence. For example, one study demonstrated that up to a third of HIV/BD individuals had antiretroviral (ARV) adherence rates less than 50% [7], with another reporting only about a third of HIV/BD individuals were adherent (i.e., 90%) to their psychotropic medications [8]. Of note, although still largely suboptimal, adherence to ARV medications appears to be overall greater than adherence to psychotropic medications in HIV/BD individuals [8], suggesting that there may be distinct behaviors and/or psychosocial, environmental, and cognitive factors associated with psychiatric medication adherence.

Of ecological relevance, psychotropic nonadherence in individuals with BD can result in greater manic and depressive symptomology [9], relapse, hospitalization, and suicide [8,10], as well as increased HIV transmission-related behaviors (e.g., unsafe sex) [11]. Furthermore, among BD individuals co-affected by HIV, it appears that nonadherence to psychiatric medications may be related to antiretroviral nonadherence [10]. Therefore, persons with co-occurring HIV and BD may represent a particularly vulnerable clinical group for psychotropic nonadherence and are therefore an important target for further characterization and intervention.

Among HIV+ individuals, difficulties with adherence to antiretroviral (ARV) therapy are associated with multiple factors, including demographics (e.g., younger age), co-occurring psychiatric disorders (e.g., bipolar disorder), alcohol/substance abuse, psychosocial variables (e.g., low perception of health/high distress), and low literacy and neurocognitive impairment [12,13]. Yet, despite the high prevalence of mental health disruption and its known adverse impact on ARV adherence, there is a paucity of studies in the HIV literature exploring factors that may impact *psychotropic* adherence. Interestingly, work among individuals with serious mental illness suggests that there are indeed a unique set of factors associated with psychiatric medication-taking behaviors compared to those observed for medical conditions; for example, among individuals with BD, psychotropic adherence demonstrates strong associations with patient belief systems (e.g., perceptions and beliefs regarding BD), the illness (e.g., frequency of symptoms), medications (e.g., perceived efficacy), and the treating physician (e.g., physician relationship) [9,14]. Integration and exploration of these and other factors may therefore be especially important in understanding and identifying points of intervention for psychotropic medication behaviors among complex medical and psychiatric populations.

The current study examined data from HIV+ individuals with bipolar disorder enrolled in a randomized-controlled text-messaging program to increase ARV and psychotropic adherence. As reported in Moore et al. [31], participants in the text-messaging condition significantly improved their ARV dose timing (i.e., took ARV closer to designated dosing time) compared to an active control group. However, the text-messaging intervention did not demonstrate any significant impact on psychotropic adherence behaviors. Our study here aimed to better understand and delineate the nature of psychotropic nonadherence among HIV+ individuals with bipolar. By establishing the factors that are most strongly affecting psychotropic adherence among HIV+ individuals with serious mental illness, more specialized and targeted treatments can be developed, possibly lowering the health-care burden associated with nonadherence in this group (e.g., psychiatric hospitalization, noncompliance with HIV treatments, disability; 15].

Methods

Participants

Participants were enrolled in a pilot text messaging intervention study at the UCSD HIV Neurobehavioral Research Program (HNRP) designed to improve medication adherence among HIV/BD individuals. Clinico-demographic characteristics of our study sample are outlined in Table 1.

Inclusion criteria were age 18 years or older, documented HIV infection, bipolar disorder type I or II via the Composite International Diagnostic Interview [16], and an active prescription of at least one antiretroviral (ARV) and one psychiatric medication to treat BD. Exclusion criteria were diagnoses of a psychotic spectrum disorder (e.g., schizophrenia), neurological conditions known to impact cognitive functioning (e.g., stroke), or a diagnosis of a mood disorder due to a general medical condition or with manic features (i.e., not primarily bipolar disorder). The UCSD Human Research Protection Program approved the current study. Participants provided written informed consent to participate.

Medication Event Monitoring System (MEMS)

The Medication Event Monitoring System (MEMS, AARDEX, Sion, Switzerland) uses a medication bottle cap with a microprocessor that records the date and time the cap is removed, and tracked medication adherence to a “sentinel” bipolar psychiatric medication over the 30-day study period.

The sentinel medication was the primary mood stabilizer defined by published clinical guidelines [17]. Specifically, the following hierarchy, based on estimation of the agent’s sensitivity to missed dosing, was used in choosing the mood stabilizing medication: lithium > valproate > carbamazepine > lamotrigine > most frequently dosed selective serotonin or noradrenaline reuptake inhibitor.

The outcome variable derived from MEMS was percent adherence during the study period [i.e., (# of bottle openings)/(# of prescribed doses)*100%]. Adherence reports were adjusted by a verbal review with participants at the follow-up visit to correct for any openings that

were done when medication was not taken. Additionally, we examined “adherent” rates using a 90% cut-score.

Psychiatric History Questionnaire

A psychiatric history questionnaire was administered to assess details of previous mood disorder diagnoses (e.g., age of diagnosis, onset of symptoms), previous psychiatric hospitalizations, and history of suicide attempts.

Current Mood Symptoms

Severity of current manic symptoms was assessed via the Young Mania Rating Scale (YMRS; range 0 to 60) [18], while the Beck Depression Inventory-II (BDI-II) assessed current depressive symptoms [19]. Higher scores indicated greater current symptomology.

Neurocognition

A comprehensive neuropsychological battery was administered to assess seven domains of functioning most affected by HIV and BD. These domains include executive functioning, speed of information processing, attention/working memory, verbal fluency, motor coordination, and episodic learning and recall. See Table 2 for a list of neurocognitive test per domain. The best available normative standards were used, correcting for effects of age, education, sex, and ethnicity, as appropriate [20]. Test scores were converted to demographically-corrected T-scores using available computer programs. Mean T-scores, per neurocognitive domain and globally, were used in the current analyses.

Prospective memory was assessed using the Memory for Intentions Screening Test (MIST; 21]. The MIST is a 30-minute, 8-trial, performance-based test that requires participants to accurately respond (verbal versus action) at different time intervals (long versus short delay) when presented with different cues (time versus event). Between cue-delays, participants complete a word search puzzle distractor task. Consistent with other studies [22], time- and event-based, scores were derived and analyzed in the current study.

Self-Reported Medication Management

Perceived medication management abilities were assessed via the Beliefs Related to Medication Adherence questionnaire (BERMA; 23). The BERMA is a 43-item self-report measure that assesses three domains: “Dealing with Health Professionals”, “Medication Management Efficacy” and “Attitudes About Medications”. The Total BERMA score was used in the current study as an overall indicator of reported medication/healthcare management skills.

Medication Attitudes

Attitudes toward psychotropic medications were assessed using the Drug Attitude Inventory (DAI; [24]). The DAI is a 30-item self-report questionnaire, which assesses the perceived beliefs and effects of medication taking behaviors (e.g., “Taking medication will prevent me from having a breakdown”). Higher scores indicate more positive attitudes toward taking medications.

Neuromedical

Participants also completed a comprehensive neuromedical evaluation, including a physical, blood analysis (e.g., CD4 count), and a review of medical and medication history. HIV serostatus was determined by enzyme-linked immunosorbent assays, and confirmed by a Western blot test.

Results

Psychotropic Adherence

Overall, HIV/BD individuals demonstrated a mean adherence rate of 78.6% to their psychotropic medications. Using a <90% adherence cut-score, 56.0% of our sample evidenced nonadherence across the 30-day study period.

Predictors of Psychotropic Adherence

Using an alpha of $p < 0.10$, we explored the univariable predictors of psychotropic adherence in HIV/BD (see Table 3). Demographically, Spearman's rho correlation revealed that only younger age ($\rho = 0.30$, $p = 0.04$) was associated with poorer adherence. In terms of psychiatric functioning, more severe current depressive symptoms ($\rho = -0.37$, $p = 0.008$), and a greater number of previous suicide attempts ($\rho = -0.33$, $p = 0.02$) and psychiatric hospitalizations ($\rho = -0.25$, $p = 0.08$) were each associated with poorer psychotropic medication adherence among HIV/BD individuals. Neurocognitively, poorer performance on time-based prospective memory ($\rho = 0.25$, $p = 0.10$), executive functions ($\rho = 0.24$, $p = 0.098$), and working memory ($\rho = 0.27$, $p = 0.067$) abilities were associated with worse adherence. Of note, better verbal fluency skills were unexpectedly associated with worse psychotropic adherence ($\rho = -0.29$, $p = 0.04$). Finally, regarding individual medication beliefs, more negative attitudes toward medications (DAI; $\rho = 0.25$, $p = 0.084$) and more negative self-beliefs regarding medication management and adherence abilities (BERMA; $\rho = 0.27$, $p = 0.064$) were associated with worse psychotropic adherence. Participant intervention group assignment (i.e., texting vs. control condition) was not associated with any of the above noted variables, including overall psychotropic adherence (p 's > 0.10). Other demographic factors (i.e., education, ethnicity), manic symptoms, HIV disease severity indicators (i.e., current and nadir CD4 count, plasma viral load, duration of infection, AIDS diagnosis), pill burden (total number of pills prescribed per day), substance use history, age of onset of manic symptoms, or age of BD diagnosis were not associated with psychotropic adherence (p 's > 0.10).

In order to determine which variables in combination may be most strongly associated with psychotropic adherence among HIV/BD individuals, we conducted a multivariable linear regression model. To reduce the overall number of predictors in our model, we used an *a priori* method to select the univariable candidate predictors ($p < 0.10$) that represented each area of functioning (i.e., one conceptually representative variable per domain as indicated by the Methods headings). Our final model included age, current depressive symptoms (BDI-II), attitudes toward medications (DAI), beliefs regarding medication management (BERMA), and executive functioning, and accounted for 25.9% (Adj. R^2) of the variance in overall psychotropic adherence (see Figure 1; $p = 0.003$). Greater current depressive symptoms ($p = 0.030$) and more negative attitudes toward medications ($p = 0.049$) were most

strongly, independently associated with poorer psychotropic adherence. The model held the same pattern of significance when texting group status ($p=0.75$) was included.

Post-hoc Analysis

Given the strong, independent association between neurocognition and antiretroviral adherence within the HIV literature [13], yet the unexpected weak contribution of neurocognition to psychotropic adherence observed here, we aimed to better understand the nature of this relationship in the current sample. We explored a model examining neurocognition (i.e., executive functions T-score), our strongest mood predictor (i.e., BDI-II), and their interaction on psychotropic adherence. We found this model alone accounted for 24.3% of the variance in psychotropic adherence ($F(3,45)=6.1$, $p=0.001$), with a significant interaction between executive functions and depressive symptoms (t ratio=2.09, $p=0.042$). Pairwise analyses using executive functions $T<40$ and BDI-II 14 as cut-points, indicated that those HIV/BD individuals who demonstrated executive dysfunction and more severe current depressive symptoms ($n=8$) showed the poorest psychotropic adherence (54.2% adherent; $p=0.004$; Figure 2).

Discussion

Although numerous studies exist exploring the factors that impact adherence to antiretroviral medications, there is a gap in the literature describing the nature of psychotropic adherence among individuals with HIV. Given the importance of adherence to psychiatric medications among HIV+ individuals with serious mental illness (e.g., increased mood symptoms leading to HIV transmission risk behaviors) and the observed poorer adherence rates to psychotropics (versus ARVs) among HIV/BD individuals [8], the current study aimed to further elucidate this topic. We found overall adherence to psychotropic medications to be suboptimal among HIV/BD participants at only 78%. Of note, only about half of the cohort reached the 90% cut-point of psychotropic adherence across the 30-day study period; those who fell below the 90% adherence cut-point averaged 64% adherence. Of clinical importance, not only can poorer psychotropic adherence lead to greater mood symptomology, but also HIV+ individuals who are less adherent to psychotropic medications, tend to demonstrate poorer ARV adherence as well [25]. Therefore, the observed low rates of adherence have important implications for quality of life at the individual level, and also significant public health repercussions for vocational productivity, psychiatric hospitalizations, disability, and HIV treatment outcomes [15].

Given the generally low adherence rates observed, we aimed to determine which factors may be contributing to these behaviors. At the univariable level, younger HIV/BD individuals with more severe current and past psychiatric problems, poorer neurocognitive abilities, and lower self-efficacy and beliefs regarding medication-taking demonstrated worse psychotropic adherence. These factors represent a convergence of variables known to be related to medication adherence among singly affected BD (i.e., self-beliefs and perceptions, [26], and psychiatric symptoms; [9]) and HIV+ individuals (i.e., younger age, psychiatric distress, neurocognitive impairment, and negative self-beliefs [13, 7]). However, there is some divergence as well. Notably, substance use is consistently associated with

nonadherence in both HIV and BD literatures, but, in the current study, histories of substance use disorders did not emerge as a significant predictor [13,28]. However, both literatures suggest that *current* abuse and dependence may be the most robust predictor of medication nonadherence [29], which we were unable to examine due to lack of variability (n=2 current substance abuse/dependence). The lack of association between HIV disease severity and psychotropic adherence may, at least partly, represent our relatively healthy HIV cohort; that is, in the current cART era, HIV infection can be well-managed as a chronic illness, in which case factors such as neurocognitive impairment and psychiatric distress, instead of disease severity, may become more prominent and influential features impacting the daily lives of these individuals.

In our multivariable model, we found greater current depressive symptoms and negative attitudes toward medications were the strongest, independent factors associated with psychotropic adherence difficulties after controlling for other contributing variables. Unlike what is observed in ARV management, neurocognitive impairment on its own was not uniquely predictive of psychotropic adherence among HIV/BD individuals. However, neurocognition, particularly executive dysfunction, does appear to moderate the relationship between mood and psychotropic adherence; HIV/BD individuals with greater executive dysfunction and depressive symptomology evidenced the worst psychotropic adherence. This finding may indicate behavioral evidence of the postulated increased neural burden on the frontostriatal systems manifested among HIV/BD participants; that is, the greater the frontostriatal dysfunction (as demonstrated by greater executive dysfunction and depression), the poorer the psychotropic adherence. These emerging findings reveal a pattern of adherence-related predictors that evidence some parallels with the HIV ARV literature (e.g., age, neurocognition), but also reflect important psychiatric contributions (e.g., medication beliefs) to psychotropic adherence in this comorbid population.

Our findings have important implications for treatment approaches in this vulnerable population. Given that there may be a cyclical relationship between depressive symptoms and psychotropic adherence (i.e., greater mood symptoms leading to worse adherence, and worse adherence leading to greater mood symptoms), it may be especially advantageous to recommend behavioral treatments for mood dysregulation (e.g., psychotherapy) in individuals with HIV/BD to improve psychotropic adherence (via symptom reduction). Of note, one recent study found that among HIV+ individuals with comorbid depression, psychotropic adherence mediated the relationship between depressive symptoms and antiretroviral adherence [25]. Taken together, this may suggest that direct interventions aimed at increasing psychotropic adherence may be particularly fruitful in both alleviating mood symptoms and HIV health outcomes among individuals with HIV and serious mental illness. In our cohort of HIV/BD individuals, poor self-efficacy and negative beliefs regarding medications (e.g., “It is unnatural for my mind and body to be controlled by medications”) were also strongly associated with poorer adherence. Psychoeducational trainings directed at teaching the goals (e.g., symptom reduction) and mechanisms (e.g., altering neurochemistry) by which psychotropic regimens work may also be especially warranted. These findings also suggest the importance for clinicians to establish a collaborative environment and patient “buy-in” regarding psychotropic regimens among HIV+ individuals with serious mental illness, in order to potentially enhance adherence

outcomes from the outset. Lastly, integrative approaches targeting monitoring and compensatory strategies in the context of depression treatment (e.g., treatment diary tracking symptoms and adherence) may be especially fruitful for individuals with executive dysfunction. Of note, better verbal fluency skills were unexpectedly associated with worse psychotropic adherence. It is conceivable that increased verbal fluency represented potential subclinical hypomania symptoms, which adversely impacted adherence; however, given our lack of variability in manic symptoms this relationship did not emerge. Another explanation may be that this was a spurious chance finding (i.e., type I error). These study findings would clearly need to be replicated in the future in order to better determine the veracity and/or mechanisms driving this relationship.

The current study also has limitations. For example, our cohort of HIV/BD participants was generally healthy and psychiatrically well-managed (only 3 participants with YMRS>14), which limits the generalizability of the current findings to patients with more severe HIV or psychiatric disease status. Also, given that this is a cross-sectional study, we cannot determine causality between psychotropic adherence and the variables examined here. In fact, those participants observed to be nonadherent over the study period may have always been nonadherent to their psychotropic regimen (i.e., not necessarily a *decline* with greater depressive symptoms or negative attitudes). It is plausible (and likely) that the effects of mood and attitudes on adherence are, in fact, bidirectional. Additionally, we had a fairly small sample size (n=50), which may have limited our power and increased the possibility of type II error. Of note, however, individuals with HIV+ and co-occurring bipolar disorder are a difficult-to-reach population and the current data represent one of the largest samples of its kind.

Our study represents one of the first attempts to characterize psychotropic adherence among HIV+ individuals with serious mental illness, and begins to identify important risk factors that may be contributing to nonadherence in this population. Given that depressive symptoms are the most common intractable symptom for individuals with BD and one of the highest comorbidities among HIV+ individuals, our study continues to support the important downstream consequences of affective problems for functional outcomes. Future studies that intervene at these pivotal points are warranted in order to continue to improve treatment outcomes.

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Figure 1.

Effect sizes (absolute standardized beta values) demonstrating the unique contribution of each predictor to psychotropic adherence among HIV/BD individuals in final multivariable linear regression model.

Note. BDI-II = Beck Depression Inventory-II; BERMA = Beliefs Related to Medications Survey; DAI = Drug Attitude Inventory; Exec Fxn = Executive Functioning T-score.

* $p < 0.05$

Figure 2. HIV/BD individuals with greater executive dysfunction and current depressive symptoms demonstrated the poorest psychotropic adherence.

Note: EF=executive functions; imp=impaired T<40; nml=normal T ≥ 40; BDI-II=Beck Depression Inventory-II; High/Low split = 14.

Table 1

Clinical characteristics of the study cohort (n = 50).

	Mean (SD), % (n), or Median (IQR)
Demographic	
Age, y	47.1 (9.7)
Education, y	13.1 (2.6)
Gender (% M)	88% (44)
Race (% Caucasian)	54% (27)
Psychiatric	
Beck Depression Inventory-II	15.8 (12.4)
Young Mania Rating Scale	4.7 (6.0)
Age of depressive symptoms onset	19.1 (10.0)
Age of manic symptoms onset	25.7 (11.0)
Age of Bipolar diagnosis	36.6 (10.4)
# Previous psychiatric hospitalizations	3.0 (3.7)
# Previous suicide attempts	1.3 (1.9)
Lifetime substance use disorder	78% (38)
Current substance use disorder	4% (2)
HIV Disease Characteristics	
Current CD4	583 (310, 912)
Nadir CD4	200.5 (97, 362)
% Detectable Plasma viral load	14.6% (7)
Duration of infection, months	190.3 (92.0)
Neurocognition	
Global *	44.8 (7.1)
Verbal *	47.2 (9.7)
Executive Functions *	46.6 (9.8)
Speed of Information Processing *	45.8 (8.3)
Learning *	40.9 (8.7)
Memory *	41.3 (9.9)
Motor *	42.1 (11.3)
Working Memory *	44.2 (11.8)
MIST Summary score	34.5 (8.9)
MIST Time-based Total score	5.1 (1.9)
MIST Event-based Total score	6.3 (1.4)
Medication adherence	
% Psychotropic adherence (30-day)	78.4% (26.7%)
BERMA, Total score	73.7 (12.9)

	Mean (SD), % (n), or Median (IQR)
Drug Attitude Inventory (DAI), Total score	5.8 (4.2)
Pill burden (total # pills/day)	13 (10, 17.3)

* Mean T-score values, demographically-corrected for age, education, gender, and race (i.e., Caucasian and African-American).

Note. MIST = Memory for Intentions Screening Test; BERMA = Beliefs Related to Medication Adherence

Table 2

Neuropsychological tests per domain.

Cognitive Domain and Test	
<u>Speed of Information Processing</u>	
	WAIS-III Digit Symbol
	WAIS-III Symbol Search
	Trail Making Test, Part A
<u>Learning and Memory (2 domains)</u>	
	Hopkins Verbal Learning Test – Revised
	Brief Visuospatial Learning Test – Revised
<u>Abstraction/Executive Functioning</u>	
	Wisconsin Card Sorting Test (64-item)
	Trail Making Test, Part B
<u>Verbal Fluency</u>	
	Controlled Oral Word Association Test
	Category Fluency (Animals)
<u>Attention/Working Memory</u>	
	WAIS-III Letter-Number Sequencing
	PASAT-50
<u>Motor</u>	
	Grooved Pegboard Test (Dominant & Non-dominant)

Note. WAIS-III = Wechsler Adult Intelligence Scale - Third Edition; PASAT-50 = Paced Auditory Serial Addition Test – channel 50;

Table 3

Correlation table (Spearman's rho) indicating significant ($p < 0.10$) univariable predictors of psychotropic adherence among persons with HIV/BD.

	% Psychotropic Adherence	
	<i>Spearman's rho</i>	<i>p-value</i>
Age	0.30	0.04
BDI-II	-0.37	0.008
# Suicide Attempts	-0.33	0.02
# Psych Hospitalizations	-0.25	0.08
MIST Time-based Total	0.25	0.10
Executive Functions T-score	0.24	0.10
Working Memory T-score	0.27	0.10
Verbal Fluency T-score	-0.29	0.04
BERMA Total	0.27	0.06
Drug Attitude Inventory	0.25	0.08

Note. BDI-II = Beck Depression Inventory-II; MIST = Memory for Intentions Screening Test; BERMA = Beliefs Related to Medications Survey.
Bolded indicates variables included in final multivariable regression model.