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Age-Related Differences in Medication Adherence, Symptoms, and Stigma in Poorly-Adherent Adults with Bipolar Disorder

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Abstract

Objective—We present a secondary analysis of data reporting differences in medication adherence, psychiatric symptom severity, and internalized stigma levels in older (age ≥ 55 years) vs. younger (age < 55 years) adults with bipolar disorder (BD) and poor medication adherence.

Methods—Data used for this analysis came from 184 participants in an NIMH-funded randomized controlled trial (RCT), comparing a customized adherence enhancement (CAE) intervention intended to promote BD medication adherence with a BD-specific educational program (EDU). At screen, study participants were ≥20% non-adherent with BD medications as measured by the Tablets Routine Questionnaire (TRQ). Psychiatric symptoms, functional status, and internalized stigma were measured using validated scales.

Results—Older adults had significantly lower anxiety disorder comorbidity ($p<0.01$ for one or more anxiety disorders), depressive symptom severity scores ($p=0.011$), and self-stigma scores ($p=0.001$) compared to their younger counterparts. In the analyses evaluating change over time in TRQ between older and younger participants by treatment arm (i.e. CAE and EDU), there was a significant finding of interaction between time, age group, and treatment arm ($p = 0.007$).

Conclusions—Older adults may be less anxious and depressed, with less self-stigma compared to younger people with BD and poor adherence. With respect to medication adherence, older individuals in EDU appear to do less well than younger individuals over time.

Keywords

medication adherence; bipolar disorder; age groups; stigma

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Introduction

Poor medication adherence in people with bipolar disorder (BD) is common and associated with a number of risk factors that may impede medication-taking (1). Younger age is a reported risk factor for medication non-adherence in individuals with BD (1, 2). The literature on the association between adherence and symptoms is conflicting (3). Patients with bipolar depression may lack motivation to engage in care, while manic patients may skip medication in order to prolong euphoria, or may simply be too distracted to stay on track with medications. Individuals with impaired functioning may be unable to prioritize medication-taking in the midst of other life-demands. Additionally, self-stigma in BD patients is well-documented (4–6), and could have negative effects on self-care including medication treatments (7). Stigma experienced by BD patients may have tangible implications on quality of life, social dysfunction, and even suicidality (8–10), while older adults may be especially sensitive to stigma associated with mental illness (11–12). Lastly, while previous analyses demonstrate that a customized adherence enhancement (CAE) program targeted to mixed-age poorly adherent adults with BD increases medication adherence and functional status compared to a BD-specific educational program (EDU), whether the impact of specific adherence promotion efforts may differ for different age groups has not been studied (13). Given demographic changes that project an increase in both proportions and absolute numbers of people with serious mental illnesses such as BD, as well as concurrent aging of the population, findings applicable to this vulnerable patient population may have practical implications for clinical care.

This secondary analysis from a completed randomized controlled trial (RCT) comparing two interventions in poorly adherent patients with BD evaluated medication adherence, psychiatric symptom severity, and internalized stigma levels in older (age ≥55 years) vs. younger (age <55 years) adults. We aim to elucidate the impact that age may have on medication adherence, symptom severity, and stigma levels in poorly adherent adults with bipolar disorder. Additionally, we intend to further characterize the effectiveness of two interventions intended to augment medication adherence in this unique patient population, by accounting for age and evaluating for adherence over time in each age subgroup. Based on prior literature, we hypothesize that older adults will have improved medication adherence, similar symptom severity, and decreased stigma levels compared to their younger counterparts. We further hypothesize that CAE may have a more sustained benefit than does EDU over time in both older and younger subgroups.

Methods

Design Overview

Data for this analysis derived from a prospective, 6-month NIMH-funded RCT comparing CAE to promote BD medication adherence with EDU in 184 poorly adherent individuals with BD. The RCT has been described in detail elsewhere (13). Study inclusion criteria were 1) diagnoses BD type I or II confirmed by Structured Clinical Interview for DSM-IV (SCID-IV), 2) duration of illness of at least two years, 3) treatment with at least one mood-stabilizing medication (i.e. lithium, anticonvulsant, or antipsychotic mood stabilizer), and 4) ≥20% non-adherence with prescribed BD medication. We chose an age 55 cut-off to

differentiate younger (n=144) vs. older (n=40) sub-groups within the RCT sample given a recent consensus recommendation to consider the fact that people with BD, on average, lose one to two decades of life compared to the general population (14). In the RCT, assessments were conducted at screening, baseline, 10 week, 14 week, and 6 month (24 week) follow-up. The study was approved by the local Institutional Review Board (IRB), was registered at ClinicalTrials.gov (identifier: NCT00183495) and completed from October 2012 to July 2017. For this secondary analysis, we compared demographic and clinical variables relevant to BD, medication adherence, BD symptoms, and stigma levels in older vs. younger groups at baseline and longitudinally (at each follow-up assessment time-point).

Demographic and clinical variables relevant to BD were assessed at baseline. BD diagnosis and psychiatric comorbidity were identified on the SCID-IV. Key outcomes in the original RCT included adherence, BD symptoms, and functioning.

Medication Adherence

Adherence was measured with the Tablets Routine Questionnaire (TRQ). The TRQ is a validated self-report measure that identifies proportion of days with missed doses in the past 7 days (past-week) and in the past 30 days (past-month) (15). Lower scores (a smaller proportion/percentage n of missed medication) represent better adherence, while higher scores (a larger proportion/percentage of missed medication) represent worse adherence. In this RCT, past-week and past-month TRQ were assessed for each BD maintenance medication prescribed for ≥3 months. For individuals who were on more than one BD medication, an average TRQ was calculated.

Psychiatric Symptoms and Functioning

BD symptoms were measured using the Montgomery–Åsberg Depression Rating Scale (MADRS) (16), the Young Mania Rating Scale (YMRS) (17), and the Brief Psychiatric Rating Scale (BPRS) (18). Participants were also rated with Clinical Global Impression (CGI) (19). Global Assessment of Functioning (GAF) was used to measure functional status (20).

Additional Variables of Interest

Attitudes regarding internalized, self-stigma were assessed with the Internalized Stigma for Mental Illness scale (ISMI). This validated tool provides data on five subscales including: Alienation, Stereotype endorsement, Discrimination experience, Social withdrawal, and Stigma resistance (10). Additional secondary evaluations included the Drug Attitudes Inventory (21), the composite index of the Addiction Severity Index (ASI) (22–23), and a standardized treatment alliance scale (24).

Data Analysis

To evaluate for age-related differences in change over time in TRQ, BPRS, and GAF in the entire sample, both treatment arms (CAE plus EDU) were combined, and younger vs. older sub-groups were compared. Mann-Whitney U test or t-test was used to analyze continuous variables. Chi-square or Fisher's Exact Test was used for categorical variables. Because TRQ, BPRS, and GAF were key outcomes of interest in the original RCT, the longitudinal

evaluation in the age sub-group analysis also focused on the TRQ, BPRS, and GAF variables. To evaluate for age-related differences in change over time in TRQ in each treatment arm (i.e. CAE vs. EDU), a mixed binary logistic longitudinal analysis was conducted on indicators of whether or not TRQ past month was less than or equal to 20%. Autoregressive autocorrelation of order one was assumed, with subject-level random intercepts. Covariates included main effects for age, treatment, and time, as well as three-way interaction terms involving age, treatment, and time. Mixed longitudinal models for BPRS and GAF were fit with the same effects and interaction terms. Because of the limited sample size, we did not add additional covariates into the models. For this analysis, a two-sided type I level of significance of 0.05 was adopted for all tests.

Results

BASELINE FINDINGS

Sample Characteristics—As noted in Table 1, in our sample, 40 of 184 participants were age 55 years or older. A statistically significant difference was noted in age of BD onset. Older participants had significantly lower anxiety disorder comorbidity compared to younger participants. The younger subgroup of participants was balanced evenly between genders, whereas the older subgroup skewed more female. A greater proportion of older individuals were female, married, and more likely to be prescribed additional medications for non-psychiatric conditions. There was robust representation of racial minorities (African-Americans) in both older and younger sub-groups. No other significant demographic differences were noted between the two age groups.

Medication Adherence—There were no statistically significant differences at baseline noted in past-week and past-month adherence with BD medications between older and younger participants.

Psychiatric Symptoms and Functioning—There were no significant differences in YMRS, BPRS, and GAF scores between the two groups at baseline. At baseline, older adults had significantly lower MADRS scores than their younger counterparts and significantly lower CGI, indicating comparatively lower depressive and overall symptom severity, respectively.

Other Clinical Variables—With regard to self-stigmatizing attitudes, older adults had significantly lower ISMI scores than their younger counterparts, indicating relatively lower internalized stigma. These findings remained significant in four out of five of ISMI's subscales: Alienation, Stereotype endorsement, Discrimination experience, and Social withdrawal. Only age-related differences in the subscale of Stigma resistance were not significant. The older sample had fewer problems with substance abuse. Attitudes towards medication and alliance with clinicians were similar between older and younger groups.

LONGITUDINAL FINDINGS

Medication Adherence, Psychiatric Symptoms, and Functional Status—In the analyses evaluating change over time between older and younger participants in the

combined group (i.e. CAE *plus* EDU), there was no significant difference in TRQ, BPRS, and GAF. There were no significant findings of interaction between time and age group when analyzed globally, regardless of treatment arm assignment at baseline.

In the analyses evaluating change over time in TRQ between older and younger participants by treatment arm (i.e. CAE and EDU), there was a significant finding of interaction between time, age group, and treatment arm ($p = 0.007$) such that older individuals had worse adherence over time in the EDU intervention arm than did their younger counterparts; however, there was no significant finding of interaction between time and age group in the CAE treatment arm. For BPRS and GAF, there were no significant findings of interaction between time, age group, and treatment arm.

Discussion

This age sub-group analysis from an RCT comparing two interventions intended to improve medication adherence in poorly adherent patient with BD found some baseline and longitudinal differences in younger (age <55 years) vs. older (age ≥55 years) patients. Demographic and clinical baseline characteristics (including adherence levels) variables were mostly similar; however, findings that differ suggest that older patients may have more social support, less depression and anxiety, and less self-stigma compared to younger individuals in spite of the fact that both age groups are poorly adherent. The finding of lower anxiety comorbidity in older BD participants is consistent with prior literature; however, our prevalence rate of 56.4% for one or more anxiety disorders is higher than what has been previously reported in the geriatric BD population (25–26). Depressive symptom severity was somewhat lower in the older vs. younger groups.

Several studies have addressed stigma in individuals with mental illness, including BD (4–6, 9, 10, 27), and demonstrate moderate-to-high internalized stigma (4–6, 28). However, to our knowledge, no other studies have reported on stigma differences by age in people with BD who are willing to acknowledge poor adherence. Perhaps older adults with BD and poor adherence have learned to develop coping skills and live with their illness over time. Despite poor medication adherence and experiencing illness for many years, this subset of older adults with BD demonstrate capacity for recovery even in later-life. This adds to the limited body of research supporting that later-life recovery is achievable with BD (30).

It has previously been reported that while individuals randomized to both CAE and EDU adults (of all ages) had improvements in TRQ and in GAF, these improvements in the CAE arm were significantly better than in the EDU arm in this RCT (13). To assess the effects of CAE vs. EDU *by age*, the same variables were analyzed by treatment arm and showed no difference in symptom (BPRS) or functional (GAF) outcomes. However, with respect to change in medication adherence (TRQ), older individuals in EDU appear to do less well than do younger individuals in EDU over time. This might suggest that CAE has more persistent benefits across the lifespan than does EDU; however, since the original RCT was not powered to determine CAE vs. EDU effects by age, these conclusions remain speculative. This potential age-related difference in outcome may be explained by CAE's customized approach to patient-specific variables and adherence barriers. This may be

particularly important to older individuals. Older people have more complicated drug treatment regimens and have had their illness for a longer duration. Perhaps the customized approach that discusses specific medications and different ways of coping with BD could have been more helpful with older adults' more complex psychiatric and medical care regimens.

Limitations of this study include its short duration, single-site setting, subjective adherence evaluation, and a sample that may not adequately represent the greater BD population. The sample used in this analysis is from an RCT of patients with poor adherence, and not a randomly sampled from a BD population. Similarly, the majority of participants in both the younger (64.6%) and older subgroups (75.0%) were African-American. Racial differences may play a role in our findings; previous studies have described differences between African Americans and whites with bipolar disorder with respect to medication adherence (31), affective symptoms (32), and "culturally biased self-perceptions" (31). Because of these demographic constraints, our sample does not represent a typical clinical population and is difficult to generalize to broader populations. This study does not include the full spectrum of older people with BD; findings apply to this cohort, but not necessarily to a more general BD population. Also, we observed several differences between the older and younger subgroups in baseline demographics that limit our findings' generalizability. For this analysis, we did not further stratify our sample by age of onset of BD. As a result, our sample includes six participants (3%) reporting late-onset BD, defined as first manic episode at age 50 years or later (14). One of these participants was stratified into the younger subgroup, and five of them into the older subgroup. Late-onset BD is usually considered a subgroup with etiology and psychopathology that may vary from that of adults with typical-onset BD. Because of its proportion of participants with late-onset BD (12.5%), the older adult subgroup, as a small sample, may not be sufficiently homogeneous to compare with the younger one. Lastly, the older adult subgroup in our sample may represent a "survivor cohort," such that adults with BD that reach age 55 years and older may be selectively "healthier" than their younger counterparts, especially in the poorly adherent population. It is reasonable to consider that adults with BD who survive into later adulthood represent those with better coping skills and self-esteem, and less medical comorbidity, to begin with. Despite these limitations, our findings suggest that even older adults with poor adherence may demonstrate capacity for recovery in BD, and that adherence enhancement approaches may be helpful to this population. Future efforts should further explore how CAE can be further refined to meet the needs of older people with BD and poor adherence.

Conclusion

This secondary analysis from an RCT comparing two interventions in poorly adherent patients with BD found that older adults may be less anxious and depressed, with less self-stigma compared to younger people with BD and poor adherence. CAE is a behavioral intervention that may yield sustained benefit with respect to medication adherence in adults with BD who are age 55 and older compared to EDU.

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Table 1.

Differences in older and younger study participants

Variable	Older Participants (N)	Mean (SD) or N (%)	Younger Participants (N)	Mean (SD) or N (%)	p-value
Gender	40		144		
Male		20 (50.0)		38 (26.4)	**<0.01**
Female		20 (50.0)		106 (73.6)	
Age Mean (SD)	40	60.28 (3.11)	144	43.82 (8.84)	**<0.001**
Race N (%)					
African-American	40	30 (75.0)	144	93 (64.6)	0.38
White		9 (22.5)		41 (28.5)	
Other		1 (2.5)		10 (6.9)	
Hispanic N (%)	40	0 (0.0)	144	6 (4.2)	0.22
Education (years) Mean (SD)	39	13.28 (2.37)	143	12.5 (2.35)	0.07
Marital status					
Single, never married	39	14 (35.9)	144	84 (58.3)	
Married/co-habiting		9 (23.1)		18 (12.5)	**0.04**
Separated/Divorced/Widowed		16 (41.0)		42 (29.2)	
Employment N (%)					
Employed	39	3 (7.7)	143	16 (11.2)	
Unemployed		2 (5.1)		39 (27.3)	**<0.01**
Disabled		33 (84.6)		77 (53.8)	
Other		1 (2.6)		11 (7.7)	
BD diagnostic type N (%)					
BD-I	40	29 (72.5)	142	113 (79.6)	0.23
BD-II		11 (27.5)		29 (20.4)	
Age of BD Onset Mean (SD)	40	33.13 (14.12)	142	21.45 (10.49)	**<0.001**

Variable	Older Participants (N)	Mean (SD) or N (%)	Younger Participants (N)	Mean (SD) or N (%)	p-value
Current comorbid disorders N (%)					
Alcohol	37	2 (5.4)	134	16 (11.9)	0.20
PTSD	35	3 (8.6)	125	61 (48.8)	**<0.001**
OCD	39	6 (15.4)	137	19 (13.9)	0.77
Generalized anxiety	39	9 (23.1)	137	33 (24.1)	0.12
No. of psychiatric meds Mean (SD)	40	1.55 (0.78)	144	3.00 (1.95)	0.86
No. of non-psychiatric meds Mean (SD)	40	1.96 (1.92)	144	1.60 (0.88)	**<0.01**
Charlson comobidity index total Mean (SD)	40	0.53 (1.18)	144	0.28 (0.91)	0.98
TRQ for BD medications (past week) (mean, SD)	34	37.25 (29.06)	111	42.97 (30.81)	0.34
TRQ for BD medications (past month) (mean, SD)	34	38.48 (26.31)	112	40.84 (27.51)	0.66
One or more anxiety disorders (N, %)	39	22 (56.4%)	139	109 (78.4%)	**<0.01**
Two or more anxiety disorders (N, %)	39	16 (41.0%)	139	80 (57.5%)	**0.05**
MADRS (mean, SD)	40	14.93 (8.20)	144	18.87 (8.70)	**0.01**
CGI (mean, SD)	40	3.08 (1.07)	144	3.47 (0.96)	**0.03**
YMRS (mean, SD)	40	7.63 (5.38)	144	8.15 (4.98)	0.56
BPRS (mean, SD)	34	34.24 (6.15)	113	35.05 (7.31)	0.56
GAF (mean, SD)	40	61.18 (8.71)	144	59.01 (8.50)	0.16
Drug Composite Score—ASI	40	0.02 (0.04)	140	0.04 (0.06)	**0.02**
Treatment alliance	27	30.74 (6.56)	84	30.37 (6.22)	0.757
Stigma for Mental Illness Scale	40	61.95 (12.67)	144	69.27 (11.54)	**0.001**
Alienation	40	13.00 (5.06)	143	14.89 (4.15)	**0.017**
Stereotype endorsement	40	11.28 (3.23)	144	13.06 (3.24)	**0.002**
Discrimination	40	9.98 (3.58)	141	12.08 (3.41)	**0.001**

Variable	Older Participants (N)	Mean (SD) or N (%)	Younger Participants (N)	Mean (SD) or N (%)	p-value
Social withdrawal	39	12.28 (4.24)	142	14.19 (4.19)	**0.013**
Resistance	40	15.48 (2.55)	141	15.16 (2.23)	0.450
DAI	40	6.98 (2.34)	144	7.04 (1.73)	0.84

Mann-Whitney U used in non-parametric continuous variables; chi-square in categorical; t-test in normally distributed continuous variables; Fisher's exact for small N comparisons (i.e. Hispanic)