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The Relationship between Medication Attitudes and Medication Adherence Behavior in Adults with Bipolar Disorder

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Abstract

Research determining the relationship between medication attitudes and adherence and reliable measures of medication attitudes are needed. Psychometric properties of the Attitudes toward Mood Stabilizers Questionnaire (AMSQ) in bipolar subjects and the relationship between medication attitudes and adherence, measured by the self-reported Tablets Routine Questionnaire (TRQ) were examined. Inclusion criteria included mood stabilizer treatment and 20% medication non-adherence. Measures were given pre- and post-treatment. Average age was 47 years; majority was female (69%), African American (67%), and unmarried (53%). AMSQ's test-retest reliability was $\rho=0.73$ ($p<0.001$). AMSQ correlated with TRQ ($r_s=0.20$, $p<0.01$) at baseline. Factor analysis identified three factors: Positive/Favorable Attitudes, Negative/Critical Attitudes, Unintentional Non-adherence. Change in AMSQ across time correlated with change in TRQ. The AMSQ is valid psychometrically and is sensitive to change. Medication attitudes are related to adherence behavior. Interventions should include targeting specific domains of medication attitudes, such as illness knowledge.

Keywords

medication attitudes; bipolar disorder; medication adherence

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Introduction

Poor adherence to medication treatment is a serious and prevalent problem in the treatment of Bipolar Disorder (BD). Studies report that between 20% and 60% of people with BD are non-adherent, often resulting in poor treatment outcomes (Lingam & Scott, 2002; M. Sajatovic, Valenstein, Blow, Ganoczy, & Ignacio, 2007; Scott & Pope, 2002a). Research examining reasons for non-adherence in BD has found that non-adherence can be related to beliefs or attitudes regarding medication treatment (Chang, Sajatovic, & Tatsuoka, 2015; Harvey, 1991; Rosa et al., 2007). Specifically, negative attitudes toward medication and negative attitudes toward bipolar disorder are important predictors for poor treatment adherence (Arvilommi et al., 2014; Casaletto et al., 2016; Levin, Krivenko, Howland, Schlachet, & Sajatovic, 2016).

Attitudes that have been associated with poor adherence include being uncomfortable with having one's mood controlled by medication, unwillingness to take medication generally, low self-efficacy for medication-taking behavior, fear of dependence on medications, denial of illness severity, concern about medication side effects, and the belief that medication is not needed when a person is not symptomatic (Chang et al., 2015; Devulapalli et al., 2010; Levin et al., 2016; Scott & Pope, 2002a). Given the significant role that attitudes play in adherence behavior, they appear to be an important treatment target.

Interventions aimed to modify medication attitudes have the potential to improve medication adherence and, in turn, reduce psychiatric symptoms and other negative treatment outcomes (Sajatovic et al., 2002). Conversely, when psychiatric symptoms are reduced, it may also become easier to maintain adherence, thus reducing the likelihood of relapse. Thus, it is important to have reliable instruments to assess attitudes towards medication among patients with BD, and, moreover, to see if these instruments correspond to actual medication-taking or adherence behaviors.

Previous efforts have examined the relationship between change in medication attitudes and adherence behavior among patients with BD. Harvey (1991) reviewed the literature and determined that existing medication attitude measures were lengthy, not disorder-specific, and not clinically oriented (Harvey, 1991). Thus, the Lithium Attitudes Questionnaire (LAQ) was developed as a rapid screening instrument for use in intervention programs that look to improve lithium treatment adherence (Harvey, 1991). The LAQ is a 19-item, self-report questionnaire whose questions were developed based on clinical experience and suggestions from colleagues and alternates questions that elicit positive versus negative experiences with lithium (Harvey, 1991). The items were based on schizophrenia literature, and therefore did not address attitudes towards mania specifically (Johnson & Fulford, 2008). The items were originally organized into 7 subscales derived on clinical grounds including: opposed to continuing lithium treatment (items 1, 10, 12, 17); therapeutic effectiveness of lithium not accepted (items 6, 19); concern about side effects (items 3, 7); difficulty maintaining pill-taking routines (items 4, 11, 14, 18); denial of illness severity (items 2, 9, 15); subcultural attitudes opposed to drug treatment (items 5, 8, 13), and dissatisfaction with factual knowledge of lithium (item 16). The side effects, subcultural attitudes, and difficulty maintaining a treatment regimen subscales were most relevant for understanding attitudes

towards lithium (Harvey, 1991). Validation of the LAQ through factor analysis was not conducted on the original LAQ.

In subsequent studies, the same 19 LAQ items were utilized to look at attitudes toward mood stabilizers in general, not just lithium (J. B. Levin et al., 2014; Sajatovic, Ignacio, et al., 2009; Scott & Pope, 2002a) and the measure was renamed The Attitudes toward Mood Stabilizers Questionnaire (AMSQ). Scott and Pope (2002) maintained the 7 subscales consisting of the same items but modified the subscale names to the following: 1) General opposition to prophylaxis, 2) Denial of therapeutic effectiveness, 3) Fear of side effects, 4) Difficulty with medication routines, 5) Denial of illness severity, 6) Negative attitudes toward drugs in general, and 7) Lack of information about mood stabilizers (Scott & Pope, 2002a). However, validation of the modified version of the instrument was not carried out and a number of the subscales were made up of as few as one or two items.

In this two-step study, Analysis 1 evaluated the psychometric properties of the AMSQ and Analysis 2 set out to further examine the relationship between medication attitudes and self-reported medication adherence as measured by the Tablets Routine Questionnaire (TRQ) both before and after an intervention aimed to improve medication adherence. Taken together, results of the analyses are expected to be useful to clinicians and researchers interested in targeting medication adherence in BD.

Methods

These data are part of a larger NIMH-funded randomized controlled trial (RCT) testing Customized Adherence Enhancement (CAE), a psychosocial intervention intended to promote BD medication adherence, versus an educational control (EDU) who received psychoeducation about bipolar disorder more generally in poorly adherent individuals with BD. A detailed description of this larger study and the CAE (N=92) and EDU (N=92) interventions are described elsewhere (Sajatovic et al., 2018). Study inclusion criteria included having either type I or type II BD as confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, Gibbon, Spitzer, & Williams, 2002), BD for at least two years duration, treatment with at least one evidence-based medication to stabilize mood for at least six months (lithium, anticonvulsant, or antipsychotic mood stabilizer), and 20% or more of days with missed doses for current bipolar medication treatment for either the past week or past month as measured by the Tablets Routine Questionnaire (Scott & Pope, 2002b). The 20% cutoff is based on the expert consensus guidelines on adherence in patients with serious mental illness (Velligan et al., 2009). Demographic and clinical data including substance abuse history were collected via an interview-based demographic questionnaire and the SCID. Past week non-adherence was utilized because recall for shorter periods is likely to be more accurate. Study inclusion criteria were purposely broad to be generalizable to real-world patients with BD. Only individuals who were unable to participate in study procedures, unable or unwilling to provide informed consent, and those at immediate risk of harm to self or others were excluded.

The study was approved by the local Institutional Review Board and all study participants provided written informed consent. Data were collected between October 2012 and July 2017.

Measures

Tablets Routine Questionnaire (TRQ) —This self-report measure identifies non-adherence for the past 7 and 30 days (Peet & Harvey, 1991; Scott & Pope, 2002b). It has been shown to correlate with objective measures of past week and past month non-adherence and has been shown to associate strongly with lithium levels (Scott & Pope, 2002a). The percentage of days with missed doses of a given medication was assessed for each foundational oral bipolar medication prescribed for 3 months. For individuals who were on 1 foundational medication, an average was calculated to gather information on the full BD treatment regimen. We did not track non-adherence to antidepressant drugs as they are often prescribed sporadically to target acute symptoms and are not considered to be maintenance medication for bipolar disorder.

Attitudes toward Mood Stabilizers Questionnaire (AMSQ) —The AMSQ is a modification of the Lithium Attitudes Questionnaire (Harvey, 1991) which evaluates an individual's attitudes towards mood-stabilizing medication. The AMSQ is a 19-item self-report questionnaire with a yes-no format. Higher scores represent more negative medication attitudes. Test-retest reliability for the original 19 items of the LAQ ranges from 57.6 % to 96.6% (Jennifer B Levin et al., 2014; Scott & Pope, 2002a). When completing the AMSQ, participants were informed that the questions referred to their attitudes regarding foundational mood stabilizers defined as maintenance treatment with lithium, anticonvulsant or antipsychotic medication.

Rating of Medication Influences Scale (ROMI) Noncompliance subscale—The ROMI is a measure of attitudes toward medication treatment and has been shown to be a reliable measure for identifying health beliefs as well as reasons for treatment non-adherence (Weiden et al., 1994). An abbreviated version of the ROMI consisting of only the Noncompliance subscale was administered. These items represent reasons for non-adherence, with higher total scores representing more negative attitudes. In a sample with schizophrenia, the ROMI Reasons for Noncompliance subscale correlated moderately with other attitude measures, had adequate inter-rater reliability, and had a Cronbach's alpha of 0.55, indicating a moderate degree of multidimensionality (Weiden et al., 1994). In a BD population, less adherent patients had higher mean scores on ROMI Noncompliance subscale (Devulapalli et al., 2010).

Drug Attitudes Inventory (DAI) —This 10-item self-report questionnaire used to measure attitudes towards medication (Awad, 1993) is relatively unaffected by psychiatric symptom severity (Sajatovic et al., 2002). The DAI was originally developed to assess the attitudes and subjective experience of patients with schizophrenia being treated with antipsychotic medications. However, the scale has been widely utilized with other seriously mentally ill populations receiving psychotropic medication (Sajatovic & Ramirez, 2003). The DAI is a simple, true-false format questionnaire that assesses domains of patients'

attitudes, including positive and negative experience, locus of control, and attitudes towards health. Higher scores represent more positive attitudes. This shortened version of the DAI-30 correlated strongly with the DAI-30 in a population with schizophrenia (Nielsen, Lindström, Nielsen, & Levander, 2012).

Psychiatric symptom severity—The Brief Psychiatric Rating Scale (BPRS) measures global psychopathology (Leucht et al., 2012; Overall & Gorham, 1962), the Montgomery-Asberg Rating Scale (MADRS) measures depression symptoms (Montgomery & Asberg, 1979), and the Young Mania Rating Scale (YMRS) measures mania symptoms (Young, Biggs, Zeigler, & Meyer, 1978). Total score on the BPRS ranges from 18 to 126, total scores on the MADRS range from 0–60, and total score on the YMRS ranges from 0–56 with higher scores indicative of more severe symptoms.

Assessments including TRQ, AMSQ, ROMI, DAI, BPRS, MADRS, and YMRS were completed at Screen, Baseline (1 week after screen), V1 (6 weeks post-baseline), V2 (12 weeks post-baseline), and V3 (24 weeks post-baseline).

Data analyses

In Analysis 1, test-retest reliability and construct validity of the AMSQ were evaluated. A factor analysis of the AMSQ was conducted, and the AMSQ total score and its factors were correlated with measures of adherence and symptoms. Finally, test-retest reliability was carried out on the resulting factors. Based on our use of the AMSQ in previous studies, we hypothesized that the AMSQ would have strong test-retest reliability, would positively correlate with the ROMI Noncompliance subscale, negatively correlate with the total score on the DAI, and that the AMSQ subscales, as identified statistically through factor analysis, would correlate with adherence as measured by the TRQ and validated symptom measures including the BPRS, MADRS, and YMRS at baseline.

In Analysis 2, we further explored the relationship between medication adherence attitudes and medication adherence behaviors. We first examined whether AMSQ total at baseline was associated with TRQ at two follow-up time points. Additionally, we examined whether change in the AMSQ total score and its subfactors were associated with change in the TRQ, other attitude measures, and symptom measures following an intervention with a psychoeducation component emphasizing the role of medication in the treatment of BD (both the CAE and EDU groups had such a component). We hypothesized that: 1) AMSQ total at baseline (BL) would correlate significantly with TRQ at V1 (6 weeks) and V3 (24 weeks), and 2) Change in total AMSQ and its subfactors would significantly correlate with change in TRQ between BL to V1, BL to V3, and V1 to V3, and change in total AMSQ would significantly correlate with MADRS, YMRS, and BPRS between BL and V3.

Analysis 1.—Sample demographics and clinical characteristics were summarized with descriptive statistics. Test-retest reliability was assessed by computing a Pearson correlation between the AMSQ total score at screening and the score at baseline (one week later). We chose this time point as we expected that it was unlikely to change dramatically yet long enough that the items would not be too easily recalled. We did not look at test-retest reliability at other time points given that participants were receiving an intervention that was

likely to impact their medication attitudes. Construct validity was examined by correlating total AMSQ at BL with the ROMI Noncompliance subscale and total DAI score. The factor structure of the AMSQ was examined using factor analysis to identify which linear components exist within the data and how a particular variable might contribute to a certain factor. A parallel analysis/Monte Carlo simulation on the factor analysis was run with 1000 random cases, with a 95% significance (p value of 0.05) to determine the number of factors. Based on Hayton et al.'s (Hayton, Allen, & Scarpello, 2004) guidelines, we retained three factors. Two-tailed Spearman and Pearson correlations, t-tests, and one-way analyses of variances (ANOVAs) between the total AMSQ score and demographic variables, adherence (TRQ), other measures attitude measures (ROMI and DAI), and clinical variables (BPRS, MADRS, and YMRS) at baseline were performed to assess the construct validity of the AMSQ.

Spearman and Pearson correlations were then performed between each AMSQ factor and DAI, ROMI, and TRQ as well as the symptoms measures including BPRS, MADRS and YMRS at baseline. Finally, test-retest reliability was calculated for each of the factors.

Analysis 2.—Spearman correlations were run to evaluate the relationship between AMSQ total at BL and TRQ at both V1 and V3 due to non-normality of the TRQ distribution. Then, partial correlations, controlling for BPRS total score at V3 and MADRS total score at V3, were run to determine if change in past week and past month TRQ were significantly correlated with change in AMSQ. Change was calculated by subtracting the BL values from the V3 values. Spearman and Pearson correlations were used to determine if change in AMSQ total score and its factors at baseline was correlated with change in adherence (as measured by TRQ), change in other attitude measures (ROMI and DAI) and change in symptoms as measured by MADRS, YMRS, and BPRS at BL, V1 and V3. All statistical analyses were run on the total sample and comparisons were not made between the two treatment groups. Statistical analyses were performed using IBM SPSS Statistics 24.

Results

Table 1 summarizes baseline sample demographic and clinical characteristics. The majority of the sample was female, African American, and unmarried. Participants were on evidence-based foundation BD medication which included lithium, the anticonvulsant drugs divalproex, lamotrigine, oxcarbazepine, gabapentin, topiramate, and second generation antipsychotic drugs. The data show that 10 (5.4%) individuals were on lithium only, 31 (16.8%) were on anticonvulsant drugs only, and 85 (46.2 %) were on antipsychotics only. All others were on a combination of medications, with the exception of two individuals; one (0.5%) who was only taking clonazepam and one (0.5%) was only taking trazadone. The mean number of medications for the 56 individuals (30.4%) who were taking multiple BD drugs was $M = 2.22$ ($SD = 0.52$). The average number of BD maintenance medications for the entire sample at baseline was 1.55 ($SD = 0.79$), median = 1.00. Average screen TRQ score indicates 55.15% of days had missed doses in the past week.

Analysis 1.

The one-week test-retest reliability of the total score was $r=0.73$, $p<0.001$. Parallel analysis and factor analysis resulted in a three-factor solution that explained 44.9% of the variance in AMSQ scores. Table 2 lists individual items and their factor loadings after a direct oblimin rotation. We verified factor loadings for face validity. The factors were then named according to item content as follows: Positive/Favorable Attitudes (items #1, 3, 6, 8, 10, 12, 16, 19), Negative/Critical Attitudes (#2, 5, 7, 9, 13, 15, 17), Unintentional Non-Adherence (#4, 14, 11, 18).

The total AMSQ score at BL significantly positively correlated with past week TRQ ($r_s=0.20$, $p<0.01$; 95% CIs [0.05, 0.34]) and ROMI ($r=0.49$, $p<0.001$; 95% CIs [0.37, 0.61]), and negatively correlated with DAI ($r=-0.48$, $p<0.001$; 95% CIs [-0.59, -0.37]).

At BL, AMSQ total scores did not significantly correlate with age ($r=-0.11$, $p=0.16$), education ($r=-0.02$, $p=0.80$), or number of BD medications ($r_s=-0.03$, $p=0.68$). There were no significant between-group differences for overall attitudes toward mood stabilizers by gender, ($t(182)=1.30$, $p=0.20$) race, ($F(2, 181)=1.62$, $p=0.20$) or marital status ($F(4, 179)=1.14$, $p=0.34$).

As can be seen in Table 3, total AMSQ at baseline negatively correlated with DAI and positively correlated with the TRQ, ROMI, BPRS and MADRS but not YMRS. The Positive/Favorable Attitudes factor significantly negatively correlated with the DAI and positively correlated with the ROMI. The Negative/Critical Attitudes factor significantly correlated with the DAI, ROMI, TRQ, BPRS, and MADRS. Finally, the Unintentional Non-adherence factor significantly negatively correlated with the DAI and positively correlated with the ROMI, BPRS, MADRS, and YMRS but did not correlate with the TRQ.

Table 4 shows that at Visit 1, which immediately follows treatment, total AMSQ positively correlated with TRQ, ROMI, and MADRS but not BPRS or YMRS. The Positive/Favorable Attitudes factor did not significantly correlate with any of the measures but the Negative/Critical Attitudes factor correlated with TRQ, ROMI, and MADRS. Finally, the Unintentional Non-adherence factor significantly correlated with TRQ and ROMI.

As can be seen in Table 5, the follow-up time point (Visit 3), total AMSQ negatively correlated with DAI and positively correlated with TRQ, ROMI, BPRS, MADRS, and YMRS. The Positive/Favorable Attitudes factor negatively correlated with the DAI and positively correlated with the BPRS and MADRS. The Negative/Critical Attitudes factor significantly correlated with the ROMI, BPRS, MADRS, YMRS and TRQ while negatively correlating with the DAI. The Unintentional Non-adherence factor negatively correlated with the DAI and positively correlated with the ROMI, TRQ, and MADRS.

The test-retest reliability of the three factors were $r(182)=0.85$, $r(182)=0.55$, and $r(182)=0.59$ ($p<0.001$ for each factor) for Positive/Favorable Attitudes, Negative/Critical Attitudes, and Unintentional Non-adherence, respectively.

Analysis 2:

Total AMSQ at the time of BL significantly correlated with the past week TRQ at V1 ($r_s(128) = 0.18$, $p = 0.03$; 95% CIs [0.04, 0.33]) and TRQ V3 ($r_s(145) = 0.19$, $p = 0.02$; 95% CIs [0.02, 0.34]. Change in past week TRQ between BL and V3 and change in AMSQ between BL and V3 was significantly correlated when controlling for BPRS and MADRS at V3 ($r(142) = 0.17$, $p = 0.04$). Similarly, the change in past month TRQ and change in AMSQ of the same timepoints was significantly correlated via partial correlations, controlling for BPRS and MADRS at V3 ($r(142) = 0.26$, $p = 0.002$).

When correlating AMSQ total change between BL and V3, with change in MADRS, YMRS, and BPRS total scores, we found there were no significant correlations with change in MADRS score ($r = 0.10$, $p = 0.26$), change in YMRS score ($r = 0.04$, $p = 0.65$), or change in BPRS score ($r = 0.14$, $p = 0.09$). However, there were significant correlations between change in AMSQ total score and change in DAI ($r = -0.46$, $p < 0.001$), as well as change in AMSQ total score and change in ROMI ($r = 0.40$, $p < 0.001$).

The change in total AMSQ did not significantly correlate with change in TRQ from BL to V1 ($r(125) = 0.10$, $p = 0.26$; 95% CIs [-0.07, 0.28]), yet did significantly correlate with change in TRQ from BL to V3 ($r(144) = 0.25$, $p < 0.01$; 95% CIs [0.09, 0.40]) and from V1 to V3 ($r(121) = 0.28$, $p < 0.001$; 95% CIs [0.12, 0.44]).

The change in AMSQ Negative/Critical Attitudes significantly correlated with change in TRQ from BL to V1 ($r_s = 0.17$, $p = 0.054$), BL to V3 ($r_s = 0.31$, $p < 0.001$), and from V1 to V3 ($r_s = 0.25$, $p = 0.004$). The change in AMSQ Positive/Favorable Attitudes did not significantly correlate with change in TRQ from BL to V1 ($r_s = -0.4$, $p = 0.66$), BL to V3 ($r_s = 0.04$, $p = 0.65$), V1 to V3 ($r_s = 0.01$, $p = 0.90$). Finally, the change in AMSQ Unintentional Non-adherence did not significantly correlate with change in TRQ from BL to V1 ($r_s = 0.09$, $p = 0.29$), BL to V3 ($r_s = 0.23$, $p < 0.01$), and from V1 to V3 ($r_s = 0.23$, $p < 0.01$).

Discussion

To the best of our knowledge, this is the first descriptive study to evaluate the psychometric properties and relationship to adherence behaviors of the AMSQ in poorly adherent patients with BD. The results show that the AMSQ has strong psychometric properties including moderate to high test-retest reliability as well as moderate construct validity. Findings suggest the AMSQ can be used to identify patient attitudes that correspond to actual medication-taking behavior among poorly adherent patients with BD Type I or Type II.

In contrast to the original measure's seven subscales which were clinically derived, with constituent items ranging from as few as one to up to four items per subscale, the factor subscales of the AMSQ were quantitatively derived in this analysis. The factor analysis yielded three discrete factors: Positive/Favorable Attitudes (8 items), Negative/Critical Attitudes (7 items), and Unintentional Non-adherence (4 items). These three factors suggest that there are three distinct subscales within the AMSQ. While two of these factors appear to be a direct result of medication attitudes, the third factor comprised of forgetting and poor routines may be indirectly impacted by attitudes. For example, individuals who are

ambivalent about medications may be less inclined to be attentive to times that they need to take medications or put in place external cues that might help them remember to take medications. The AMSQ evidenced good convergent validity based on its positive relationship with the ROMI Noncompliance Subscale and negative association with the DAI, both established measures of medication attitudes (Hogan, Awad, & Eastwood, 1983; Nielsen et al., 2012; Weiden et al., 1994), as well as its significant relationship with symptom measures including the BRPS, MADRS and self-reported medication non-adherence. As would be expected, more negative attitudes about mood stabilizers is associated with more severe psychiatric symptoms including depression and worse adherence to mood stabilizer medications. The lack of a significant relationship between medication attitudes and the YMRS is likely due to the fact that manic symptoms were generally very low in our sample. It is possible that findings would be different in a sample that exhibits more severe manic symptoms. Furthermore, the fact that the sample was comprised of individuals with either Bipolar Type I or Type II with minimal manic/hypomanic symptoms may have influenced the results.

The psychometric properties of the three subscales of the AMSQ derived from factor analysis were also shown to be good. There is evidence of moderate to high test-retest reliability with the Positive/Favorable Attitudes subscale achieving above 0.85. Given that there was a week between administrations, it is logical that the test-retest reliability coefficients for Negative/Critical Attitudes and Unintentional Non-adherence were moderate, falling in the 0.55–0.59 range. Also, the AMSQ appears to be sensitive to change as evidenced by its showing a similar change pattern to that of the DAI, an attitudes measure with a large body of research (Nielsen et al., 2012; Rej et al., 2016; Stjernswärd, Persson, Nielsen, Tuninger, & Levander, 2013; Townsend, Floersch, & Findling, 2009). Additionally, the AMSQ subscales help delineate the relationship between attitudes and adherence behavior. Given that prior to treatment only the Negative/Critical Attitudes factor correlated with medication adherence, reducing negative attitudes by improving BD knowledge is a vital target for treatment which is consistent with the adherence treatment literature (Johnson & Fulford, 2008; Levin et al., 2016; Sajatovic et al., 2011). Additionally, the relationship between AMSQ and other measures of medication attitudes appear to be largely explained by two factors prior to treatment, Positive/Favorable Attitudes and Negative/Critical Attitudes, suggesting that Unintentional Non-adherence, while considered vital by patients as a barrier to treatment adherence (Sajatovic et al., 2011), are generally not included in the construct of medication attitudes. Finally, it is the Negative/Critical Attitudes and Unintentional Non-adherence factors which are associated with increased psychiatric symptomatology pre-treatment, again supporting these areas as important treatment targets.

With respect to change between AMSQ factors and TRQ at different timepoints, change in Negative/Critical Attitudes and Unintentional Non-adherence were more strongly correlated with medication taking behavior than Positive/Favorable Attitudes. Additionally, change in Negative/Critical Attitudes was correlated with each subsequent visit, suggesting that targeting psychoeducation is important for adherence improvement. Change in Unintentional Non-adherence was also correlated with change in medication taking behavior at most time points following an adherence intervention, suggesting that in the BD population, routines is a necessary, albeit possibly insufficient treatment target. This finding is consistent with the

literature on prospective memory, or the ability to remember to engage in a behavior in the future, which tends to be impaired in those with BD due to executive functioning deficits such as planning and cognitive flexibility (Lee et al., 2010; Zogg, Woods, Saucedo, Wiebe, & Simoni, 2012). Thus, even when an individual has the intention to take medication, they might lack the planning or organizational abilities to do so consistently (Zogg et al., 2012). Sajatovic et al. also report that forgetfulness and lack of routines is the most important reason for non-adherence (Sajatovic et al., 2011) which supports the findings of the current study and suggests that in order to improve adherence in this population, interventions must take into account this cognitive deficit. Possible strategies to target Unintentional Non-adherence might include medication reminders via text or an eHealth application, use of a pillminder or other organizational device, and integrating medication taking into one's daily routine with tasks that are not forgotten (e.g. morning coffee or meal times) (Blixen et al., 2018; Levin et al., 2016).

A key finding in this study is that AMSQ and TRQ scores were significantly correlated as were the change in AMSQ and TRQ following treatment. This strongly suggests that medication attitudes (AMSQ) are related to adherence behaviors (TRQ) and that interventions aimed at modifying an individual's attitude about the importance of medication can lead to behavior change. Both the CAE and EDU interventions in the larger parent RCT (Sajatovic et al., 2018) emphasized psychoeducation on BD and the importance of medication as a necessary treatment component. While our results suggest that attitudes are an important correlate of actual behavior, the study methodology does not negate the importance of external supports that might also improve adherence behavior such as prompts or cues to remind patients to take medications or delivery systems such as long-acting medication formulations that might get around adherence barriers such as forgetting to take medication or the hassle-factor of having to take pills one or more times per day.

There are important clinical implications which can be drawn from the results of this study. First, adherence attitudes appear to comprise discrete domains that are potential targets for intervention. This finding is consistent with an ample literature base that indicates that some of the adherence attitude domains can be changed with specific treatments. For example, knowledge can be improved with targeted education. However, targeting a single domain, such as insufficient or incorrect knowledge of BD, does not by itself appear to adequately change adherence behavior (Levin et al., 2016; Sajatovic, Davies, et al., 2009). As such, integrated approaches which target specific reasons why individuals choose to take or not take their prescribed BD medication can help inform future personalized approaches to care that may optimize efficiency and efficacy.

There are several limitations and considerations which should be noted. First, since these patients were a part of a larger study for poorly-adherent individuals, this sample does not include patients who are adherent to their medication. All participants were 20% non-adherent at screen so attitude comparisons to adherent individuals was not possible. Secondly, our sample was comprised of individuals with either Bipolar I or II with few manic/hypomanic symptoms and the analyses were run on the group as a whole which may have impacted the findings. Additionally, the analyses only utilized a self-report measure of adherence. Regarding the relationship between medication attitudes and adherence, the fact

that participants were in long-term treatment and were aware that they were participating in a psychosocial adherence intervention may have impacted their report of medication attitudes as well as self-reported adherence. Also, as mentioned above, in order to determine the relationship between the AMSQ and manic/hypomanic symptomatology, future studies would need to recruit individuals in the midst of a manic/hypomanic episode. Additionally, given that the AMSQ, a modified version of the LAQ which was developed based on the schizophrenia literature, it lacks specific questions related to mania/hypomania. As such, consideration should be given to adding a couple questions to address attitudes towards medication to address elevated mood. Finally, given the complexity of the attitudes construct and the difficulty in teasing out whether forgetting and poor routines is solely a function of unintentional non-adherence or is also impacted by negative attitudes towards medication, the AMSQ may be improved by the addition of a clarifying question such as whether their attitudes or feelings about medication has made it difficult for them to remember to take their medications.

Conclusions

Given that attitudinal characteristics of non-adherent individuals have implications for the delivery of health care services which enhance and promote adherence to treatment in individuals with BD, it is vital that we have stable and valid measures for medication adherence. The AMSQ has demonstrated good psychometric properties, relates to medication taking behavior, and is sensitive to change in response to treatment. Future studies should assess the impact of using the AMSQ at baseline to identify and target individual attitudinal barriers to sustained medication adherence.

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Table 1:

Demographic and clinical characteristics of the baseline sample (N=184)

	N(%) or mean (SD)
Age (years)	47.40 (10.46)
Gender	
Female	126 (68.5%)
Male	58 (31.5%)
Education years	12.67 (2.37)
Race	
Caucasian	50 (27.2%)
African-American	123 (66.8%)
Other	11 (6.0%)
Marital status	
Single, never married	98 (53.3%)
Married	27 (14.7%)
Separated/Divorced/Don't know	51 (27.7%)
Widowed	8 (4.3%)
BPRS	34.60 (7.72)
MADRS	18.01 (8.73)
YMRS	8.04 (5.06)
AMSQ	8.70 (3.71)
DAI	7.03 (1.87)
ROMI	11.31 (4.54)
Past week TRQ	44.19 (31.16)
Age of onset of bipolar disorder	24.02 (12.34)
Lifetime number of psychiatric hospitalizations-- Median	3.00
Duration of illness, years (n=182)	23.42 (11.46), range 2 to 52

Table 2:

Factor loadings of Attitudes toward Mood Stabilizers Questionnaire items after direct oblimin rotation

AMSQ Items	Factor 1	Factor 2	Factor 3
1. I would find it perfectly acceptable to take MS for several years.	0.73		
2. I take MS now and then, whenever I feel I need to.		0.59	
3. It is definitely worth taking despite its side effects.	0.78		
4. Taking MS exactly as prescribed fits in very easily with my daily routine.			0.72
5. Finding relief from personal stress is more important than taking MS in keeping me well.		0.50	
6. I consider that MS is at present necessary for my personal well-being.	0.87		
7. I worry about possible side-effects from my MS tablets, even when I'm feeling well		0.40	
8. Most people I know would probably be in favor of my taking MS.	0.69		
9. I sometimes try to forget I have been ill by taking a break from MS tablets.		0.64	
10. I rely on my tablets and if they were stopped I would be concerned.	0.79		
11. People often have to remind me to take my MS tablets.			0.43
12. MS is just as acceptable to me when I consider the need for repeated blood tests and checkups.	0.72		
13. I often think that since MS is an artificial way to keep stable I should be able to do without it.		0.63	
14. It is very easy to remember to take MS at the right time.			0.68
15. I often doubt that my condition is sufficiently serious to justify the long-term use of MS.		0.38	
16. I have an adequate factual knowledge of MS and its effect.	0.58		
17. Being weak for several months would make me consider coming off MS.		0.49	
18. If my daily routine changes for any reason I have difficulty in remembering to take my tablets.			0.51
19. I am convinced of the beneficial effects of MS from my own personal experience of taking it.	0.84		

Table 3:

Pearson correlations between symptom and adherence measures and AMSQ at Baseline

	Total AMSQ	Medication Benefits	Poor Illness Knowledge	Medication Routines/Forgetfulness
DAI	-0.46 **, p< .001	-0.32 **, p< 0.001	-0.38 **, p< 0.001	-0.04, p= 0.61
ROMI	0.49 **, p<.001	0.19 **, p< 0.01	0.60 **, p< 0.001	0.18 *, p= 0.02
Past Week TRQ ^a	0.20 *, p< 0.01	0.09, p= 0.22	0.19 **, p< 0.01	0.12, p= 0.11
BPRS	0.24 **, p< 0.001	0.08, p= 0.26	0.24 **, p< 0.01	0.17 *, p= 0.02
MADRS	0.21 *, p< 0.01	0.07, p= 0.35	0.19 **, p< 0.01	0.19 **, p= 0.01
YMRS	0.07, p= 0.38	-0.07, p= 0.37	0.14, p= 0.67	0.16 *, p= 0.03

^aAMSQ: Attitudes toward Mood Stabilizers Questionnaire;^bDAI: Drug Attitude Inventory;^cROMI: Rating of Medication Influences Scale,^eBPRS: Brief Psychiatric Rating Scale;^fMADRS: Montgomery-Asberg Depression Rating Scale;^gYMRS: Young Mania Rating Scale

*.: significant at the 0.05 level

**.: significant at the 0.01 level

Table 4:

Pearson correlations between symptom and adherence measures and AMSQ factors at Visit 1

	Total AMSQ	Medication Benefits	Poor Illness Knowledge	Medication Routines/Forgetfulness
DAI	not given at V1			
ROMI	0.36, ** p<0.001	0.05, p= 0.60	0.51, ** p<0.001	0.30, ** p<0.001
Past Week TRQ ^a	0.41, ** p<0.001	0.22, p= 0.11	0.45, ** p<0.001	0.35, ** p<0.001
BPRS	-0.01, p= 0.89	-0.13, p= 0.14	0.11, p= 0.20	-0.07, p= 0.44
MADRS	0.29, ** p<0.001	0.09, p= 0.32	0.38, ** p<0.001	0.17, p= 0.06
YMRS	0.02, p= 0.82	-0.01, p= 0.88	0.40, p= 0.65	0.16, p= 0.19

^a AMSQ: Attitudes toward Mood Stabilizers Questionnaire;^b DAI: Drug Attitude Inventory;^c ROMI: Rating of Medication Influences Scale,^e BPRS: Brief Psychiatric Rating Scale;^f MADRS: Montgomery-Asberg Depression Rating Scale;^g YMRS: Young Mania Rating Scale

*: significant at the 0.05 level

**: significant at the 0.01 level

Table 5:

Pearson correlations between symptom and adherence measures and AMSQ factors at Visit 3

	Total AMSQ^a	Medication Benefits	Poor Illness Knowledge	Medication Routines/Forgetfulness
DAI ^b	-0.60 **, p< 0.001	-0.41 **, p< 0.001	-0.46 **, p< 0.001	-0.30 **, p< 0.001
ROMI ^c	0.37 **, p< 0.001	0.02, p= 0.81	0.62 **, p< 0.001	0.25 **, p< 0.01
Past week TRQ ^d	0.38 **, p< 0.001	0.12, p= 0.16	0.35 **, p<0.001	0.41 **, p< 0.001
BPRS ^e	0.27 **, p< 0.001	0.17 *, p= 0.04	0.23 *, p< 0.01	0.13, p= 0.12
MADRS ^f	0.36 **, p< 0.001	0.23 **, p< 0.01	0.26 **, p< 0.001	0.22 **, p< 0.01
YMRS ^g	0.25 *, p< 0.01	0.15, p= 0.08	0.23 **, p= 0.01	0.12, p= 0.14

^aAMSQ: Attitudes toward Mood Stabilizers Questionnaire;^bDAI: Drug Attitude Inventory;^cROMI: Rating of Medication Influences Scale,^eBPRS: Brief Psychiatric Rating Scale;^fMADRS: Montgomery-Asberg Depression Rating Scale;^gYMRS: Young Mania Rating Scale

*: significant at the 0.05 level

**: significant at the 0.01 level