Promoting medication adherence among patients with bipolar disorder: a multicenter randomized controlled trial of a multifaceted intervention

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Declaration of Interest

None

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Abstract

Background: The present research was aimed to investigate the efficacy of a multifaceted intervention that included motivational interviewing and psychoeducation (both for patients and their family members) to improve adherence in patients with bipolar disorder.

Method: A multicenter, cluster randomized, observer-blind, controlled, parallel-group trial was conducted in ten academic centers in Iran. Patients with BD were randomly assigned to the experimental group (EXP; n=136) or the usual care group (UC; n=134). The EXP group received five sessions of motivational interviewing and psychoeducation together with their family members. The primary outcome measure was changes in scores on the Medication Adherence Rating Scale (MARS) from baseline to 6-months post-intervention. Other outcome measures included serum levels of mood stabilizers, clinical symptoms, quality of life, as well as measures of intention, beliefs about medicine, perceived behavioral control, automaticity, action and coping planning, and adverse drug reactions.

Results: Medication adherence improved over time in both groups, but patients in the EXP group improved more (baseline score: 6.03; score at the sixth month: 9.55) than patients in the UC group (baseline score: 6.17; score at the sixth month: 6.67). In addition, patients in the EXP group showed greater improvement than patients in the UC group in almost all secondary outcomes 6 months following the intervention.

Conclusions: Multifaceted interventions that include motivational-interviewing and psychoeducation can significantly improve medication adherence and clinical and functional outcomes in patients with BD.

Trial Registration Number: The trial was registered with theClinicalTrials.gov database (NCT02241863) https://clinicaltrials.gov/ct2/show/NCT02241863

Keywords: adherence; bipolar disorder; mood stabilizer; motivational interviewing; psychoeducation

Introduction

Bipolar disorder (BD) causes significant disability in personal and social domains, and with a prevalence of 1-2%(Merikangas *et al.*, 2007), it imposes a huge burden on society. According to a recent meta-analysis, patients with BD spend more than 40% of their time ill (Forte *et al.*, 2015). Despite the fact that it is possible to control the symptoms of BD using medication, on-adherence is a substantial problem and has been reported in up to 50% of cases(Geddes and Miklowitz, 2013, Lacro *et al.*, 2002, Lingam and Scott, 2002, Scott and Pope, 2002a, b). Patients with BD show a much lower rate of routinely and consciously taking prescribed medicines (35%) than patients with, for example, schizophrenia (50-60%).Consequently, patients with BD tend to have poorer health outcomes, including lower levels of daily functioning, psychological health, and quality of life (QoL) (Dean *et al.*, 2004, IsHak *et al.*, 2012). Therefore, it is important to develop interventions that can promote medication adherence (MA).

Effective interventions are likely to be those that target modifiable determinants of non-adherence (Berk *et al.*, 2004) such as beliefs and attitudes (Berk *et al.*, 2004, Lingam and Scott, 2002, Scott and Pope, 2002a). As a result, a few studies (Bauer *et al.*, 2006a, b, Cakir *et al.*, 2009, Javadpour *et al.*, 2013) have designed behavioral interventions (e.g., behavioral therapy, family reliant treatments, psychosocial education, and interpersonal therapies) in an effort to enhance patients' adherence to medications. For example, Parsons et al. used behavioral therapy to improve MA in HIV-positive people and found reductions in substance abuse, although no significant change in MA perhaps due to the relatively small sample (Folco *et al.*, 2012). In another study on BD patients, eight sessions of psychoeducation yielded better MA and also QoL among participants in the intervention group when followed up 2 years later (Javadpour *et al.*,

2013). Other interventions designed to promote MA have focused on increasing communication and support provided by family members to patients, and this strategy is popular for the treatment of mental disorders such as schizophrenia (Rollnick *et al.,* 2008).

However, previous studies that have addressed the challenge of MA in patients with BD have been somewhat limited in their methods. To the best of our knowledge, all previous studies have only used one type of intervention (namely psychoeducation) in addition to usual care (Rouget and Aubry, 2007). The effects of psychoeducation for patients with BD and their family members have been demonstrated in many outcomes, such as MA and insight improvement and symptoms relief for people with BD (Bilderbeck et al., 2016, Hidalgo-Mazzei et al., 2016, Kallestad et al., 2016, Rouget and Aubry, 2007); care burden and distress reduction for family members (Bermúdez-Ampudia et al., 2016, Hubbard et al., 2016). However, patients with BD can differ in their responses to the same intervention (Culpepper, 2014). It is therefore possible that a multifaceted intervention that targets non-adherence from various aspects might result in better adherence. Moreover, many (but not all) previous studies (Bauer *et al.*, 2006b, Cakir *et al.*, 2009, Javadpour *et al.*, 2013) have primarily used self-reported questionnaires to measure MA. However, self-reported outcomes may be biased by social desirability effects (e.g., patients with BD may feel obligated to report that they have followed the instructions of a health professional) and / or memory problems (e.g., patients with BD may not remember whether they have taken their medication). Using objective measures of adherence, such as serum levels of mood stabilizers, can reduce the possibility of bias and provide a more accurate estimate of the effect of an intervention on MA.

The intervention was centered around motivational interviewing (MI), a client-centered approach that targets enhancement of change in attitude and behavior (Lundahl *et al.,* 2013).

Although originally developed for alcohol dependence, the use of MI has been rapidly expanded to other health-related domains. Indeed, a meta-analysis of 48 studies has shown that MI is an effective way to promote changes in behavior across multiple healthcare domains such as diabetes, obesity, smoking, and HIV treatment (Lundahl *et al.*, 2013). In recent years, MI has also been used to improve MA in conditions that require long-term commitment to treatment such as schizophrenia and acute coronary syndrome (Depp *et al.*, 2007). Nevertheless evidence on the effect of MI in improving MA in patients with BD is scarce.

In addition to MI, we also propose that interventions should include family members, because family members likely support patients with BD in taking their medications (Williams and Wright, 2014) especially in the East, where culture substantially values the family relationship (Tsai *et al.*, 2015).Furthermore, the effects of psychoeducation have been found to be promising in previous studies (Javadpour et al., 2013).

The present research tried to address the limitations of previous studies of interventions designed to improve adherence in BD by developing a multifaceted intervention and examining the effects of that intervention on self-report and objective measures of MA, as well as secondary outcomes that include potential mediators of treatment effects. Specifically, all outcome measures were assessed immediately post-intervention and 6-months later.

Methods

Design and study population

A multicenter, randomized, observer-blind, controlled, parallel-group trial was conducted in ten academic centers in Iran: Tehran (three centers), Qazvin, Ahvaz, Semnan, Zanjan, Tabriz, Zahedan and Mashahd between September 2014 and October 2016. Persian speaking patients

were eligible if they; 1) met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for bipolar I or II disorder simultaneously confirmed by the administration of Structured Clinical Interview (SCID); 2) were 18 years or older;3) were being treated with a mood stabilizer, and 4) were not attending weekly or biweekly psychotherapy. Patients were excluded if they; 1) had a DSM-IV-TR diagnosis of drug or alcohol misuse disorders (five independent researchers administered a semi-structured interview and a structured interview based on DSM-IV-TR criteria for alcohol abuse, alcohol dependence and also substance abuse excluding nicotine);2) showed evidence of severe DSM-IV-TR borderline personality;3) needed to change the type and/or the dose of a mood stabilizer;4) were pregnant or planned to be pregnant in the next year;5) were unable and/or unwilling to provide a written informed consent;6) had any organic cerebral cause for bipolar disorder(e.g. multiple sclerosis or stroke);or 7) had an intellectual disability.

All patients and their family members provided informed consent before participating in the study. The protocol was prepared in accordance with the Ottawa Statement, the Helsinki Declaration and Good Clinical Practice and ethical review committees at each of the sites approved the trial. The trial was registered in the clinicaltrials.gov registry (https://clinicaltrials.gov/ct2/show/NCT02241863).

Intervention

A multifaceted intervention was developed in an effort to improve MA and clinical outcomes. The intervention included two components: a) Psychoeducation for the patients and their family members and b) motivational interviewing. Detailed information on the intervention is shown in online Supplementary 1.

MI integrity/fidelity

To assess treatment fidelity, all sessions were recorded and transcribed. Two trained research assistants reviewed each recording to determine the proportion of the intervention elements that were covered by the facilitators. The Motivational Interview Treatment Integrity (MITI) scale was used to assess the integrity of the MI in the EXP group. Two separate aspects of treatment fidelity were taken into account: (i) Global variables (i.e., empathy, evocation, collaboration, autonomy/support, and direction) and (ii) behavior counts (i.e., giving information, asking open-ended and closed-ended questions, providing simple and complex reflections, and making other statements categorized as MI adherent or not). Detailed information on the intervention is shown in online Supplementary Table S1. Inter-rater reliability between two trained research assistances were computed by intraclass correlation coefficients (ICCs) using a two-way mixed model with absolute agreement. The ICCs were found to be adequate for global measures, behavior count and summary scores (ICCs ranged from 0.69 to 0.9, online Supplementary Table S1)

Usual Care

Patients in the usual care (UC) group received the usual advice from psychiatrists about their disease and medication. The usual care for people with severe mental illness, including patients with bipolar disorder, in Iran mental health system is mainly based on pharmacological interventions and follow-up visits to address and deal with dose adjustments, medication switch and side effects. There is no national guideline for mandatory and systematic psychosocial services such as occupational rehabilitation, supported employment, social skills education and family support. However, during last decade, there are growing interests and movements in mental health care to include these services, so the usual care mainly is medications prescription and monitoring their efficacy and side effects and informal psycho-education about social skills

and compliance to treatment may present in some occasions. The main obstacle to add the psychosocial services is said by officials to be lack of funding and human resources.

Outcomes

The primary outcome measure was MA, and secondary outcomes included beliefs and measures of psychosocial health. All outcomes were measured three times (at baseline before the intervention, and then one and six months after the intervention) using the measures described below. Clinical status was assessed using the Clinical Global Impressions-Bipolar-Severity of Illness (CGI-BP-S; (Spearing *et al.*, 1997)) and the Young Mania Rating Scale (YMRS; (Young *et al.*, 1978)) and Montgomery Åsberg Depression Rating Scale (MADRS; (Montgomery and Asberg, 1979)) were used to assess manic and depressive symptoms, respectively. The clinical measures were administrated by five psychiatrists who were blinded to the treatment allocation.

Medication Adherence Rating Scale (MARS)

The MARS was used to measure the primary outcome in the study; namely, MA. Patients were asked to rate the extent to which five statements (O'Carroll *et al.*, 2011) describing non-adherent behaviors, such as forgetting to take medicines or missing a dose, apply to them on a 5-point Likert scale (1: *always* to 5: *never*). The MARS has been shown to be relatively unaffected by social desirability effects (O'Carroll *et al.*, 2011), and the Persian translation of the MARS (Pakpour *et al.*, 2014) demonstrates unidimensionality and high levels of internal consistency (Cronbach's α=0.84).

Plasma level of mood stabilizer

Plasma levels of mood stabilizers were obtained from biochemistry laboratories at each center, and levels of three mood stabilizers were assayed: Lithium, Carbamazepine, and Sodium valproate.

Beliefs about Medicines Questionnaire - Specific (BMQ-Specific)

The BMQ-specific (Horne *et al.*, 1999) is used to assess beliefs about medications prescribed for personal use and has been shown to be correlated to adherence(Pakpour *et al.*, 2015). The measure reflects two domains (necessity and concerns) and each domain has five items that patients are asked to indicate their agreement with on a 5-point Likert scale (from 1: s*trongly disagree* to 5: *strongly agree*). The necessity domain assesses patients' beliefs about the necessity of the medication (e.g., *Without my medicines I would be very ill*), while the concerns domain examines patients' beliefs about the possible adverse effects of the medication (e.g., *Having to take medicines worries me*). Scores can range between 5 and 25, with higher scores indicating stronger beliefs about the necessity of the medication or a higher level of concern about taking the medicine, respectively. The Persian version of the BMQ has promising psychometric properties and has been used on an Iranian sample with diabetes(Aflakseir, 2012).

Intention

Patients' intention to take their medication was measured using a questionnaire adapted from Pakpour et al. (Pakpour *et al.*, 2014). Patients were asked to indicate their agreement with five statements (e.g., *I intend to take regular medication in the future*) on a 5-point Likert scale (1: *completely disagree* to 5: *completely agree*). Internal consistency of the scale was adequate (Cronbach's α=0.91).

Self-monitoring

Self-monitoring was measured by three items (e.g., *During the last week, I have consistently monitored when to take my medications,* on a 5-point scale from *not at all true* (1) to *exactly true* (5)(Pakpour *et al.*, 2015). Cronbach's α for the scale was 0.89.

Self-report Behavioral Automaticity Index (SRBAI)

The SRBAI comprises four items from Self-Report Habit Index (Gardner *et al.*, 2012), that measure the extent to which relevant behaviors are performed automatically (a key component of habit, (Orbell and Verplanken, 2010)). Each item starts with the stem *Behavior X is something…*and is followed by (1) *I do automatically*; (2) *I do without having to consciously remember*; (3) *I do without thinking*; and (4) *I start doing before I realize I am doing it* (Gardner *et al.*, 2012). All items are rated on a 5-point Likert scale (1: *disagree* to 5: *agree*).

Action and coping planning

Action planning was measured using four items: *I have made a detailed plan regarding when / where / how often / how to take medication*. Similarly, coping planning was measured using four items: *I have made a detailed plan regarding…*(1) *what to do if something interferes*; (2) *what to do if I forgot Taking my medication*; (3) *how to motivate myself if I don't feel like Taking my medication*; and (4) *how to prevent myself from being distracted*. All items measuring action planning and coping planning were rated on a 5-point Likert scale (1: *completely disagree* to 5: *completely agree*) and showed high levels of internal consistency (Cronbach's α=0.90).

Perceived behavioral control (PBC)

PBC was measured using four items on a 5-point Likert scale (1: *completely disagree* to 5: *completely agree*) that have proved internally consistent (Cronbach's $\alpha = 0.94$). Sample items include: *For me to take regular medication in the future is…* and *It is up to me to take regular medication…*

Young Mania Rating Scale (YMRS)

The YMRS contains 11 items each describing a specific mania syndrome. Patients are asked to rate how severely they have experienced each syndrome within the past 2 days. The

items include elevated mood, increased motor and activity-energy, sexual interest, sleep, irritability, speech rate and amount, language/thought disorder, thought content, disruptive/aggressive behavior, appearance, and insight. All items are rated from 0 (absent) to 4 (the highest level), and four of the items (irritability, speech, thought content, and disruptive/aggressive behavior) are double-weighted(McIntyre *et al.*, 2004, Young *et al.*, 1978) when computing the overall score.

Montgomery Åsberg Depression Rating Scale (MADRS)

The MADRS contains 10-items designed to measure depression (e.g., reduced appetite: *representing the feeling of loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat*). The MADRS is designed to be particularly sensitive to the effects of treatment (such as antidepressants) among people with mood disorders. Patients are asked to respond to each of the items on a 6-point scale and total scores can range from 0 (no symptoms of depression) to 60 (highest level of depression (Montgomery and Asberg, 1979)).

Clinical Global Impressions-Bipolar-Severity of Illness (CGI-BP-S)

The CGI-BP-S is modified from Clinical Global Impressions Scale for specific use with patients with BD. The CGI-BP-S comprises three measures to which patients are asked to respond using 7-point Likert scale. The measures evaluate: (1) The severity of illness (*Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?*); (2) change from preceding phase (*Compared to the phase immediately preceding this trial, how much has the patient changed?*); (3) change from worst phase (*Compared to the patient's worst phase of illness prior to the current medication trial or during the early titration phase, how much has the patients changed?*). A lower score on the CGI-BP-S suggests a better condition (Spearing *et al.*, 1997)

Quality of Life in Bipolar Disorder scale (QoL.BD)

The QoL.BD contains 12 items, and is designed to capture patients' subjective perceptions of BD-specific QoL. Each item asks about a specific experience in the past week (e.g., *Felt physically well*). Patients are asked to respond on a 5-point Likert scale (1: *strongly agree* to 5: *strongly disagree*), and a higher score represents a higher level of QoL(Michalak *et al.*, 2010).

Adverse drug reaction (ADR)

Adverse reactions to the prescribed medications were assessed using a questionnaire adapted from the clinical monitoring form for mood disorders(Sachs *et al.*, 2002). Patients were asked to indicate the severity of nine side effects (e.g., tremor, dry mouth, etc.) on a five-point Likert scale, ranging from *none* (0) to *severe* (4). A total score was computed as the sum of the severity of each side effect and could range from 0 to 36 with higher scores indicating more severe side effects.

Randomization and masking

In order to prevent contamination between the EXP and UC groups, centers were used as unit of randomization rather than patients. Trained professionals at each center (e.g., physicians and nurses) enrolled participants. Centers were allocated in a 1:1 ratio to either EXP or UC groups by a computer-generated list of random numbers. Five clusters were assigned to the EXP group and 5 clusters to the UC group. Figure 1 illustrates the flow of participants through the trial. Assessors, psychologists and psychiatrists were blind to the intervention status of each.

Across centers, 538 patients were referred to the trial: 43 declined to be screened for eligibility, 217 did not meet screening criteria, and we lost contact with 8. A total of 270 patients

underwent baseline assessment and 134 were randomized to the UC group and 136 to the EXP group (Figure 1). As a result, each center recruited an average of 26 patients.

Sample Size

The required sample size was calculated based on the primary outcome measure (the MARS). It was estimated that 132 patients would be needed in each condition to detect an effect size of *1 point in the MARS*, with 85% power and a significance level of 5%, assuming an intracluster correlation coefficient of 0.05, a mean cluster size equal to 27, and that 10% of the patients would be lost to follow up.

Statistical Analysis

Due to the hierarchical nature of the data (i.e., patients were nested within centers), we used multilevel linear mixed modeling to investigate the efficacy of the intervention. Three levels of analysis - time, patients, and centers – were estimated with a restricted iterative generalized least square (RIGLS) estimation. The effects of potentially confounding variables (e.g., age, education, family income, and adverse drug reactions) was measured using univariate multilevel analyses and the three variables that had *p* valueless than 0.20 (age, education, and family income) were entered into the multiple variable model. Therefore, for each model, six fixed effects were entered; an intercept term, a slope for age (years), a slope for education (years), a slope for adverse drug reaction and dummy variables for family income (reference group was low income), and condition (the UC group served as the reference group).

To decompose the interaction between condition and time, we compared the effects of condition at each time point (one and six months after treatment) on each dependent variable. The Benjamini and Hochberg false discovery rate was used to adjust p-values for multiple comparisons. In addition, Krull and MacKinnon’s three-step recommendations for conducting

mediation analyses were performed to identify potential mediators of treatment effects(Krull and MacKinnon, 1999). All tests were two sided with a significance level of <0.05 and analyses were performed on an intent-to-treat basis using MLwiN 2.27 software.

Results

Randomization Check

Table 1 summarizes the baseline and clinical characteristics of the two groups. There were no significant differences between the conditions on any of these variables. About 51% of the participants in the UC group and 55% of the participants in the EXP group were females and the mean age (*SD*) of the patients was 41.2 (6.4) years in the UC group and 41.8(8.4) in the EXP group. Mean age of onset of BD was 24 years for both groups.

Effects of the Intervention on the Primary Outcome: Medication Adherence

MA improved over time in both EXP and UC groups (Table 2). However, scores on the MARS indicated a greater improvement among patients in the EXP group: M_{baseline}= 6.03 (*SD* = 2.56) and $M_{\text{six months}}$ = 9.55 (*SD* = 3.88); than among patients in the UC group: M_{baseline} = 6.17 (*SD* = 2.90) and $M_{\text{six months}}$ = 6.67 (*SD* = 2.93). In support of this idea, after taking into account the study center, repeated measurement over time, and three potential confounding variables (age, education, and monthly family income), our multilevel mixed models showed that patients in the EXP group had significantly higher MARS scores than did patients in the UC group both one (B=3.15; p<0.001) and six months (B=3.20; p<0.001) after the intervention (Table 4).

Analysis of the objective measures of MA; namely, plasma level of mood stabilizers, indicated that patients in the UC group had slightly decreased levels at six month post-intervention of Lithium (baseline: 0.660 mmol/L; sixth month: 0.596 mmol/L), Carbamazepine (baseline: 5.580 mcg/mL; sixth month: 5.472 mcg/mL), and Sodium valproate (baseline: 41.255

mcg/mL, sixth month: 41.001 mcg/mL), suggesting that they may not have been adhering to their medication regimen. In contrast, however, patients in the EXP group had increased levels of Lithium (baseline: 0.665 mmol/L; sixth month: 0.698 mmol/L), Carbamazepine (baseline: 5.596 mcg/mL; sixth month: 6.147 mcg/mL), and Sodium valproate (baseline: 40.094 mcg/mL; sixth month: 43.048 mcg/mL), supporting the beneficial effects of the intervention on MA suggested by the self-report measure of adherence. After controlling for study center, repeated measurement, and potential confounders, Supplementary Tables S2 shows that patients in the EXP group had significantly higher plasma levels of mood stabilizers than did patients in the UC group at one month (B = 0.108 for Lithium, 1.53 for Carbamazepine, and 3.62 for Sodium valproate; $p < 0.001$), and six months (B = 0.178 for Lithium, 1.40 for Carbamazepine, and 5.28 for Sodium valproate; $p < 0.001$) post-intervention.

Effects of the Intervention on Secondary Outcomes

Almost all secondary outcomes improved significantly over time in the EXP group (see Table 2), and Tables 3 and4 show that patients in the EXP group had significantly better outcomes on all secondary measures one month and six months after the intervention, compared with patients in the UC group, except for the measure of quality of life at one month follow-up. Therefore, patients in the EXP group had stronger intentions to take their medication, believe that they had more control over so doing, that taking their medication was more automatic, and were more likely to form action and coping plans to promote MA.

There was evidence of a decrease in clinical symptoms among patients in the EXP group, relative to patients in the UC group, as shown by significant effects of group on the YMRS (B=-5.32; $p<0.001$), CGI-BP-S (B=-0.528; $p<0.001$), and MARDS (B=-4.54; $p<0.001$) measures.

Furthermore, the quality of life of patients in the EXP group improved significantly more than among patients in the UC group (B=1.17; p=0.025).

Mediation Analyses

As Supplementary Tables S3 indicates, the multifaceted intervention produced the higher rates of MA across study period. These effects were mediated by changes in beliefs about medication (i.e., beliefs about the necessity of taking the medication and concern about the possible adverse effects of the medication), intention, self-monitoring, action planning, and coping planning.

We also explored whether MA mediated the effect of the intervention on quality of life. The results of the mediation analysis indicated that there was a significant mediation effect of MA in improving patient's quality of life (Table S3). Moreover, we examined whether MARS mediated the effect of intervention on plasma levels of mood stabilizers. The results of the mediation analysis indicated that there was a significant mediation effect of MARS in improving plasma levels of mood stabilizers. The MARS was mediated between the intervention effect and improving Serum Lithium level at one month (B= 0.32; SE= 0.10; p<0.001) and six month (B= 0.42; SE= 0.07; p<0.001) follow-ups. The MARS was mediated between the intervention effect and improving Serum Carbamazepine level at one month (B= 2.46; SE= 0.36; p<0.001) and six month (B= 2.59; SE= 0.49; p<0.001) follow-ups. Finally, the MARS was mediated between the intervention effect and improving Serum Sodium Valproate level at one month (B= 2.17; SE= 0.68; p<0.001) and six month (B= 1.92; SE= 0.62; p<0.001) follow-ups.

Discussion

The aim of the present research was to assess the efficacy of a multifaceted intervention on MA and health outcomes in patients with BD. We found that a combination of brief sessions of MI, together with psychoeducation and efforts to engage family members in promoting adherence led to significant improvements in objective and self-report measures of MA, as well as in various clinical and functional outcomes compared with the usual care. Therefore, the findings of the present study may serve as a guideline for mental health clinicians when dealing with BD patients and provide a rationale for designing and implementing multifaceted interventions to improve the MA in such patients. Delivering interventions to both patients and their caregivers may provide a synergistic pattern of practices for health promotional activities.

A few prior studies have investigated whether interventions based on MI can improve MA in patients with BD. In a quasi-experimental pilot study of 21 elderly subjects with BD, Depp et al. showed that a multifaceted intervention including motivational training improved MA, as well as depressive symptoms and QoL (Depp *et al.*, 2007). However, this was only a preliminary pilot study with a simple training intervention and a limited outcome measure. Another study on patients with BD in Iran, showed the effectiveness of an intervention based on psychoeducation. This study included an 18 month follow up and measured quality of life, medication compliance as well as frequency of hospitalization showing considerable improvements in each outcome (Javadpour *et al.*, 2013).However, the study only involved one center with 108 patients the intervention only used psychoeducation and did not include family members.

In addition to MI, our intervention included other components, namely psychoeducation and engagement of a family member. Despite the importance of MA (or lack thereof) in patients with BD, a systematic review of studies testing the efficacy of interventions designed to improve

MA in BD found only five studies whose primary outcome was adherence. A meta-analysis of 18 studies showed an OR of 2.27(95%CI=1.45–3.56) for improvement in adherence in the intervention group compared to control groups (MacDonald *et al.*, 2016).To the best of our knowledge, our study is the most comprehensive study to date of a multifaceted intervention to improve the adherence in patients with BD. We found promising effects of the intervention on both self-reported and objective measures of MA. Furthermore, our findings also pointed to improvements in symptoms and QoL, which mediation analyses indicated can be attributed to improved MA.

Strengths and limitations

Our study had several strengths. First, we used both self-report and objective outcome measures to ensure the validity of our findings. Second, using multiple outcome measures targeting different domains allowed us to look at the effect of the intervention on different aspects of health and functioning. Third, we used a multilevel linear mixed model that adjusted for potential confounding variables (e.g., age) to evaluate the effect of intervention on outcomes.

Our findings should be interpreted in light of some limitations, however. First, family engagement constituted an important component of the intervention in the present research. While we deem this to be a strength of our multifaceted approach, we acknowledge that family likely plays a more significant role in individuals who live in Middle Eastern cultures than in other, more Western societies (Daneshpour, 1998). Therefore, the effect of the family engagement component of our intervention group might not necessarily be generalizable to other cultures. Second, it might be argued that the effect of our intervention is not clear beyond six months of follow-up. However, a meta-analysis by MacDonald and colleagues have shown that the effects of interventions on MA seemed to be durable for up to two years (MacDonald *et al.*,

2016). There is no reason to believe that the effects of the present intervention might not also be maintained over this period. Third, it might be argued that a longer intervention might improve adherence rates even further. However, the feasibility of such interventions also should be considered in term of time and cost as well as efficacy of short period interventions compared to those which require greater investment of resources. Finally, a natural downside to a multifaceted approach to intervention is the inability to isolate which part of the intervention was most effective. Future research might usefully adopt factorial designs that systematically manipulate and compare different components of the intervention (e.g., the intervention with and without family support) in an effort to identify the active ingredients.

Conclusion

In summary, the present findings provide robust evidence that a multifaceted intervention based on MI, psychoeducation, and attempts to engage family members can improve MA among patients with BD. The implication is that health care professionals, especially those who deal with mental health aspects of people with psychiatric disorders such as BD, may use our findings to improve MA and adjust clinical symptoms in their clients.

Figure legends

Fig. 1: The flow diagram of randomized process.

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Tables

Table 1: Baseline and Clinical Characteristics of Patients by Condition

	Mean (*SD*) or *n* (%)	
	Usual care (*n* = 136)	Experimental (*n* = 134)
Age (year)	41.2 (6.4)	41.8(8.4)
Age at onset (year)	24.3 (6.1)	24.0 (5.9)
Sex		
Male	67 (49.3%)	60 (44.8%)
Female	69 (50.7%)	74 (55.2%)
Education (year)	6.9 (3.4)	6.2 (4.0)
Duration of illness (year)	8.2 (5.6)	8.6 (5.3)
Monthly family income (US$)		
High (>1000$)	26 (19.1%)	15 (11.2%)
Intermediate (500-1000$)	78 (57.4%)	92 (68.7%)
Low (<500$)	32 (23.5%)	27 (20.1%)
Bipolar disorder type		
I	114 (83.8%)	110 (82.1%)
II	22 (16.2%)	24 (17.9%)
Living status		
Living with partner	57 (41.9%)	52 (38.8%)
Single	79 (58.1%)	82 (61.2%)
Total number of episodes	8.3 (5.7)	8.5 (6.1)
Number of hospitalizations	2.1 (0.49)	2.2 (0.54)
Mood stabilizers (Yes)		
Lithium	57 (41.9%)	56 (41.8%)
Carbamazepine	23 (16.9%)	19 (14.2%)
Sodium valproate	56 (41.2%)	59 (44.0%)
Antipsychotics (Yes)	34 (25.0%)	31 (23.1%)
Mood stabilizer monotherapy (Yes)	58 (42.6%)	54 (40.3%)
Drug dose at inclusion (mg)		
Lithium	980.6 (212.8)	970.1 (200.1)
Carbamazepine	640 (173.2)	651 (171.9)
Sodium valproate	960 (141.9)	958 (134.6)
The total numbers of taking drugs	2.3 (1.0)	2.1 (1.2)
Body mass index (kg/m^2)	26.8 (4.2)	25.9 (4.0)
Number of centers	5	5
Number of patients in each center	26.6 (3.1)	26.1 (3.4)

Note. *SD* = standard deviation.

Table 2: Descriptive Statistics for all Outcome Measures by Condition and Time

Variable	Group	Mean (*SD*)/missing n		
		Baseline	One month post-intervention	Six months post-intervention
MARS	UC	6.17 (2.90)/0	6.77 (2.85)/4	6.67 (2.93)/7
	EXP	6.03 (2.56)/0	9.53 (3.84)/1	9.55 (3.88)/9
BMQ necessity	UC	14.59 (2.31)/0	14.52 (2.20)/2	14.54 (3.01)/8
	EXP	14.43 (2.29)/1	18.69 (2.49)/2	18.64 (2.48)/10
BMQ concerns	UC	13.19 (3.97)/0	13.22 (3.92)/4	13.20 (4.13)/12
	EXP	12.90 (3.31)/0	6.04 (3.80)/1	5.90 (3.75)/9
Perceived behavioral	UC	2.58 (0.92)/4	2.61 (0.95)/3	2.56 (0.97)/8
control	EXP	2.55 (0.90)/0	2.86 (1.06)/3	2.89 (1.13)/9
Intention	UC	2.73 (0.65)/0	2.78 (0.69)/3	2.75 (0.71)/10
	EXP	2.79 (0.75)/0	3.45 (1.12)/1	3.43 (1.14)/11
Self-monitoring	UC	1.99 (0.42)/2	1.96 (0.52)/0	1.94 (0.43)/10
	EXP	2.05 (0.53)/1	2.57 (1.03)/2	2.54 (1.01)/12
Action planning	UC	1.91 (0.51)/0	1.89 (0.55)/3	1.86 (0.56)/9
	EXP	1.90 (0.54)/1	2.64 (1.17)/4	2.66 (1.34)/9
Coping planning	UC	1.67 (0.54)/0	1.64 (0.55)/4	1.65 (0.56)/9
	EXP	1.65 (0.59)/1	2.40 (1.28)/5	2.39 (1.39)/9
SRBAI	UC	1.88 (0.82)/0	1.87 (0.83)/2	1.79 (0.88)/8
	EXP	1.90 (0.83)/0	2.14 (0.90)/4	2.20 (0.93)/11
QoL.BD	UC	39.38 (9.18)/0	39.42 (9.26)/3	39.18 (9.27)/9
	EXP	39.14 (11.34)/0	40.90 (11.63)/2	43.56 (12.37)/11
YMRS	UC	15.57 (2.28)/0	15.59 (2.46)/3	15.61 (2.35)/7

	EXP	15.32 (2.76)/0	12.23 (2.19)/1	10.04 (2.01)/9
CGI-BP-S	UC	4.55 (0.65)/0	4.56 (0.61)/2	4.57 (0.47)/7
	EXP	4.60 (0.75)/0	4.52 (0.51)/2	4.18 (0.43)/9
MADRS	UC	21.82 (5.81)/0	21.37 (4.74)/2	21.28 (4.85)/7
	EXP	22.21 (5.71)/0	17.08 (7.67)/3	17.13 (7.55)/9
ADR	UC	10.03 (2.97)/3	10.00 (2.99)/6	9.98 (2.79)/9
	EXP	9.94 (2.95)/4	10.09 (2.88)/3	10.15 (2.89)/12
Serum Lithium level	UC	0.66 (0.15)/0	0.601 (0.22)/2	0.596 (0.227)/4
(mmol/L)	EXP	0.67 (0.18)/0	0.694 (0.23)/1	0.698 (0.241)/2
Serum Carbamazepine level	UC	5.58 (1.40)/0	5.496 (1.39)/2	5.472 (1.461)/1
(mcg/mL)	EXP	5.60 (1.51)/0	5.948 (1.84)/1	6.147 (1.680)/3
Serum Sodium valproate	UC	41.26 (16.45)/0	41.09 (16.73)/2	41.001 (17.746)/4
level (mcg/mL)	EXP	40.90 (18.78)/0	42.55 (18.19)/0	43.048 (19.224)/3

Note. *SD* = standard deviation. UC = usual care group. EXP = experimental group. BMQ = Beliefs about Medicines Questionnaire. SRBAI = Self-report Behavioral Automaticity Index. MARS = Medication Adherence Rating Scale. QoL.BD = Quality of Life in Bipolar Disorder scale. YMRS = Young Mania Rating Scale. CGI-BP-S = Clinical Global Impressions-Bipolar-Severity of Illness. MADRS = Montgomery–Åsberg Depression Rating Scale. ADR = Adverse drug reaction or adverse drug effect.

Table 3: Three-level Multiple Linear Regression Models predicting Medication Adherence, Intention, Perceived Behavioral Control, Automaticity of Medication Taking, Self-Monitoring, Action and Coping Planning

Variable	MARS		INT		PBC		SRBAI		SM		ACP		CP	
	B (*SE*)	*p*-value	*B* (*SE*)	*p*-value	*B* (*SE*)	*p*-value	*B* (*SE*)	*p*-value	*B* (*SE*)	*p*-value	*B* (*SE*)	*p*-value	*B* (*SE*)	*p*-value
Group (Ref: UC)	0.69 (0.61)	0.26	0.13 (0.13)	0.39	0.09 (0.18)	0.80	0.009 (0.15)	0.99	0.07 (0.15)	0.57	0.11 (0.13)	0.49	0.07 (0.12)	0.47
Time (Ref: baseline)														
One month	0.38 (0.16)	0.018	0.09 (0.04)	0.02	0.06 (0.04)	0.13	0.02 (0.04)	0.62	0.04 (0.04)	0.31	0.03 (0.04)	0.45	0.03 (0.04)	0.45
Six months	0.25 (0.16)	0.12	0.02 (0.04)	0.56	0.06 (0.04)	0.13	0.07 (0.04)	0.05	0.06 (0.04)	0.16	0.05 (0.04)	0.29	0.04 (0.04)	0.29
Group × Time														
EXP vs. UC at one month	3.15 (0.230)	<0.001	0.64 (0.05)	<0.001	0.59 (0.06)	<0.001	0.45 (0.05)	<0.001	0.55 (0.06)	<0.001	0.76 (0.06)	<0.001	0.77 (0.06)	<0.001
EXP vs. UC at six months	3.20 (0.23)	<0.001	0.60 (0.05)	<0.001	0.59 (0.05)	<0.001	0.43 (0.05)	<0.001	0.50 (0.06)	<0.001	0.78 (0.06)	<0.001	0.78 (0.06)	<0.001
Intercept	10.88 (2.15)	<0.001	2.88 (0.38)	<0.001	2.84 (0.46)	<0.001	2.29 (0.43)	<0.001	2.54 (0.32)	<0.001	2.42 (0.39)	<0.001	2.18 (0.388)	<0.001
$\hat{\sigma}^2_{st}$ (patients)	1.91 (0.62)	0.003	0.11 (0.03)	0.002	0.20 (0.06)	<0.001	0.13 (0.04)	0.002	0.15 (0.04)	<0.001	0.08 (0.03)	0.007	0.09 (0.03)	0.003
$\hat{\sigma}^2_{sc}$ (centers)	15.16 (0.94)	<0.001	0.41 (0.03)	<0.001	0.61 (0.04)	<0.001	0.57 (0.04)	<0.001	0.21 (0.02)	<0.001	0.42 (0.030)	<0.001	0.42 (0.03)	<0.001

Note. UC = usual care group. EXP = experimental group. MARS = Medication Adherence Rating Scale. INT = intention. PBC = Perceived behavioral control. SRBAI = Self-report Behavioral Automaticity Index. SM = Self-monitoring. ACP = Action planning. CP = Coping planning. ADR = Adverse drug reaction.

Table 4: Three-level Multiple Linear Regression Models Predicting Beliefs about Medication, Mania Symptoms, Severity of Illness, Depression, and Quality of Life

Variable	BMQ specific necessity		BMQ specific concerns		YMRS		CGI-BP-S		MARDS		QoL.BD		ADR	
	B (*SE*)	*p*-value	*B* (*SE*)	*p*-value	*B* (*SE*)	*p*-value	*B* (*SE*)	*p*-value	*B* (*SE*)	*p*-value	*B* (*SE*)	*p*-value	*B* (*SE*)	*p*-value
Group (Ref: UC)	0.02 (0.58)	0.97	-0.20 (0.78)	0.80	-0.10 (0.44)	0.81	-0.08 (0.16)	0.62	-0.48 (1.26)	0.71	1.21 (1.07)	0.26	0.08 (0.11)	0.46
Time (Ref: baseline)														
One month	0.07 (0.12)	0.59	-0.18 (0.19)	0.35	-0.02 (0.18)	0.91	0.01 (0.03)	0.81	-0.45 (0.23)	0.055	0.27 (0.37)	0.46	0.10 (0.07)	0.15
Six months	0.54 (0.12)	<0.001	-0.24 (0.19)	0.21	-0.04 (0.01)	<0.001	0.03 (0.03)	0.33	-0.60 (0.24)	0.012	0.031 (0.37)	0.93	0.16 (0.14)	0.25
Group × Time														
EXP vs. UC at one month	4.51 (0.17)	<0.001	-6.67 (0.27)	<0.001	-3.1 (0.01)	<0.001	-0.26 (0.05)	<0.001	-4.70 (0.33)	<0.001	0.93 (0.55)	0.09	0.14 (0.09)	0.12
EXP vs. UC at six months	4.83 (0.17)	<0.001	-6.82 (0.28)	<0.001	-5.39 (0.01)	<0.001	-0.53 (0.05)	<0.001	-4.54 (0.33)	<0.001	1.40 (0.52)	0.025	0.20 (0.12)	0.09
Intercept	15.39 (1.31)	<0.001	10.47 (1.72)	<0.001	13.41 (1.34)	<0.001	5.00 (0.373)	<0.001	24.09 (2.69)	<0.001	44.99 (4.54)	<0.001	6.68 (0.33)	<0.001
$\hat{\sigma}^2_{st}$ (patients)	2.25 (0.62)	<0.001	4.12 (1.12)	<0.001	1.20 (0.36)	0.002	0.165 (0.048)	<0.001	10.88 (2.99)	<0.001	3.92 (1.92)	0.051	0.512 (0.13)	<0.001

$\widehat{\sigma}^2_{sc}$ (centers)	4.63 (0.31)	<0.001	7.18 (0.52)	<0.001	6.35 (0.36)	<0.001	0.384 (0.025)	<0.001	19.36 (1.27)	<0.001	71.19 (4.45)	<0.001	0.42 (0.11)	<0.001

Note. UC = usual care group. EXP = experimental group. BMQ = Beliefs about Medicines Questionnaire. YMRS = Young Mania Rating Scale. CGI-BP-S = Clinical Global Impressions-Bipolar-Severity of Illness. MARDS = Montgomery Åsberg Depression Rating Scale. QoL.BD = Quality of Life in Bipolar Disorder scale. ADR = Adverse drug reaction.

CONSORT Flow Diagram

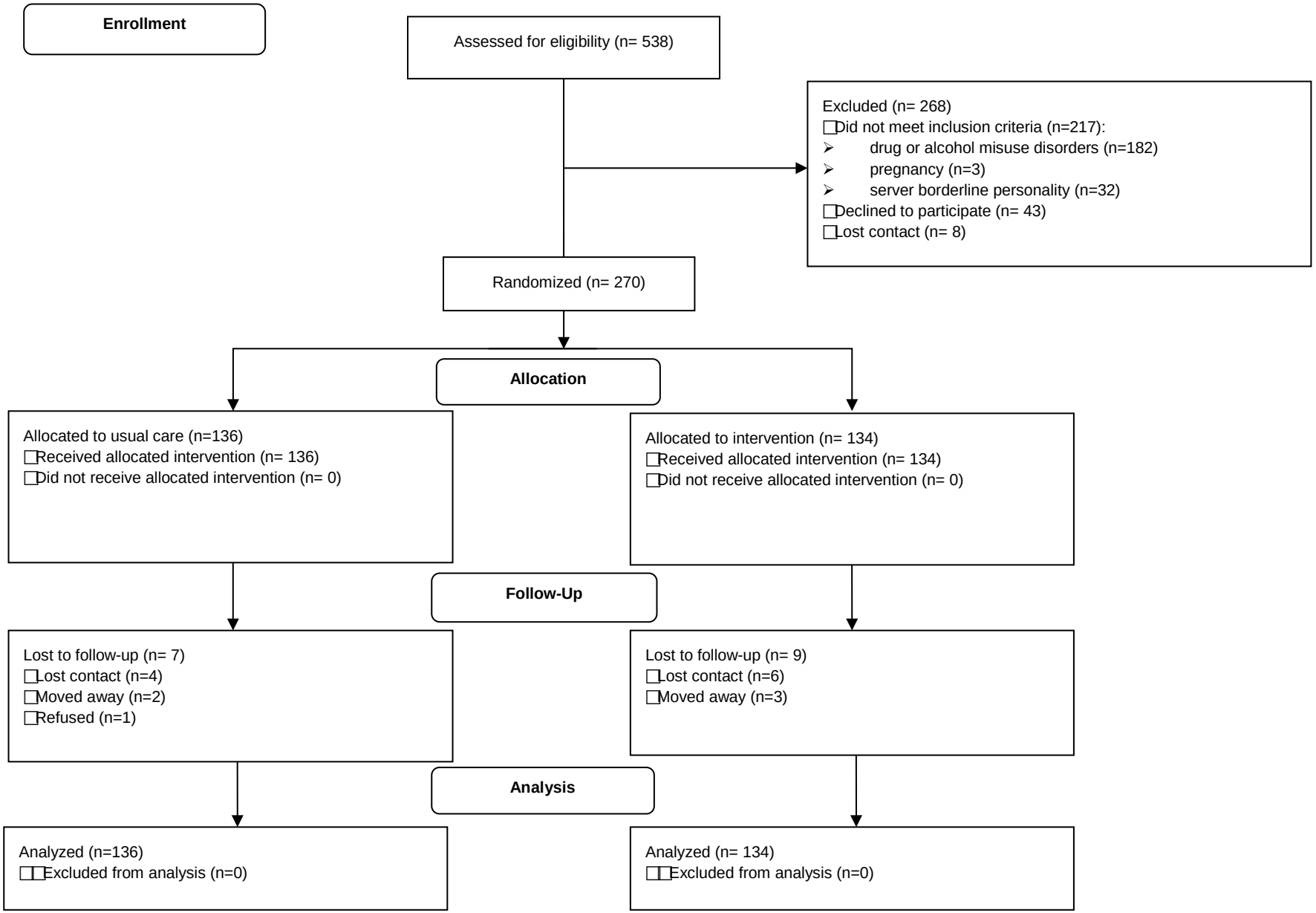

Table S1. MITI global measures, behavior counts, summary scores and interrater reliability

Measures	Mean ±SD	Minimum	Maximum	ICC
Global measures				
Evocation	3.99 (0.65)	2	5	0.69
Collaboration	3.31 (0.32)	2	5	0.71
Autonomy/support	4.02 (0.51)	1	5	0.73
Direction	3.99 (0.53)	1	5	0.79
Empathy	4.48(0.50)	1	5	0.70
Behavior counts				
Giving Information	0.34 (0.40)	0		0.81
MI-Adherent	5.47 (2.64)	0	18	0.92
MI-Non-Adherent	0.88 (0.93)	0	5	0.87
Closed Questions	12.83 (8.01)	0	32	0.76
Open Questions	8.19 (4.03)	0	30	0.81
Simple Reflections	11.61 (6.12)	0	49	0.68
Complex Reflections	100.00 (5.81)	1	30	0.80
Summary scores				
Global Spirit Rating	3.99 (0.47)	2.11	4.81	0.79
Percent Complex Reflections	50.38 (16.88)	10.01	100.00	0.76
Percent Open Questions	60.73(15.90)	20.17	100.00	0.81
Reflection-to-Question Ratio	2.55 (2.13)	0.37	19.46	0.77
Percent MI Adherent	96.68 (6.25)	50.00	100.00	0.83

Note. MI = motivational interviewing. MITI = Motivational Interview Treatment Integrity. ICC = intraclass correlation coefficient; used for testing inter-rater reliability between two raters.

Table S2. Three-level Multiple Linear Regression Models Predicting Serum Levels

Variable	Serum Lithium level		Serum Carbamazepine level		Serum Sodium Valproate level	
	B (*SE*)	*p*-value	*B* (*SE*)	*p*-value	*B* (*SE*)	*p*-value
Group (Ref: UC)	0.02 (0.04)	0.62	0.08 (0.32)	0.80	0.69 (2.14)	0.74
Time (Ref: baseline)						
One month	0.04 (0.01)	0.002	0.19 (0.11)	0.07	1.94 (0.52)	<0.001
Six months	-0.06(0.01)	<0.001	-0.26 (0.11)	0.016	2.70 (0.52)	<0.001
Group × Time						
EXP vs. UC at one month	0.15 (0.02)	<0.001	1.61 (0.15)	<0.001	3.62 (0.73)	<0.001
EXP vs. UC at six months	0.20 (0.02)	<0.001	1.40 (0.16)	<0.001	5.28 (0.74)	<0.001
Intercept	0.80 (0.09)	<0.001	6.01 (0.73)	<0.001	44.54 (8.56)	<0.001
$\hat{\sigma}^2_{st}$ (patients)	0.04 (0.003)	<0.001	0.66 (0.18)	<0.001	18.71 (8.13)	0.022
$\hat{\sigma}^2_{sc}$ (centers)	0.02 (0.002)	<0.001	1.06 (0.10)	<0.001	256.87 (15.35)	<0.001

Note. UC = usual care group. EXP = experimental group. ADR = Adverse drug reaction.

Table S3: Direct and Mediated Effects of Group on Medication Adherence and Quality of Life (QoL)

Outcome	Time (Month)	Mediator	Coefficient (SE)			
			A. Intervention effect on outcome	B. Intervention effect on mediator	C. Mediator effect on outcome	Mediated effect (=B*C)
Medication adherence	1		3.15 (0.23)**			
		BMQ necessity		4.33 (0.17)**	0.13 (0.01)**	0 55** (0.04)
		BMQ concerns		-6.67 (0.27)**	-0.07 (0.01)**	0.45** (0.08)
		PBC		0.59 (0.06)**	0.13 (0.10)	0.08 (0.06)
		Intention		0.60 (0.05)**	0.432 (0.115)**	0.26 (0.07)**
		Self monitoring		0.55 (0.06)**	0.77 (0.110)**	0.42 (0.08)**
		Action planning		0.76 (0.06)**	0.54 (0.10)**	0.41 (0.08)**
		Coping planning		0.77 (0.06)**	0.56 (0.08)**	0.43 (0.07)**
		SRBIA		0.45 (0.05)**	0.11 (0.11)	0.05 (0.05)
	6		3.20 (0.23)**			
		BMQ necessity		4.77 (0.17)**	0.12 (0.01)**	0.57 (0.05)**
		BMQ concerns		-6.75 (0.28)**	-0.06 (0.010)**	0.42 (0.07)**
		PBC		0.58 (0.05)**	0.16 (0.10)	0.09 (0.06)

		Intention		0.60 (0.05)**	0.478 (0.110)**	0.29 (0.07)**
		Self monitoring		0.50 (0.06)**	0.79 (0.113)**	0.40 (0.07)**
		Action planning		0.78 (0.06)**	0.54 (0.10)**	0.42 (0.08)
		Coping planning		0.78 (0.06)**	0.52 (0.09)**	0.40 (0.08)**
		SRBIA		0.43 (0.05)**	0.142 (0.10)	0.06 (0.04)
QoL.BD	1	Medication adherence	0.93 (0.55)**	3.15 (0.23)**	0.04 (0.02)**	0.12 (0.07)**
	6	Medication adherence	1.17 (0.52)*	3.20 (0.23)**	0.23 (0.02)**	0.72 (0.09)**

BMQ= Beliefs about Medicines Questionnaire; PBC= Perceived behavioral control; SRBIA= Self-report Behavioral Automaticity Index; QoL.BD= Quality of Life in Bipolar Disorder scale.

*$p < 0.05$

**$p < 0.01$

a) Psychoeducation

At least one family member (a spouse, partner, parent, or sibling) in the experimental (EXP) group was invited to attend two sessions of group psychoeducation in the outpatient clinic. Each session was conducted by a board-certified psychiatrist and lasted 70 minutes, with a 15-minute break. At the sessions, the family members and the patients were given information about the aetiology, symptoms, and prognosis of BD, as well as mood stabilizers, antidepressants and their possible side effects. Each family member was also provided with information about the importance of MA and the risks of discontinuing the medication. At the end of the sessions, the family members were given a booklet providing information about BD and possible drug treatments.

b) Motivational interviewing (MI)

The goal of the MI sessions was to reduce resistance and overcome ambivalence about taking medication. Patients in the EXP group attended three sessions over 1 month, each lasting 40 to 65 minutes. All sessions were held in a quiet, private, and comfortable setting inside the outpatient clinics. Seven trained and registered health psychologists delivered the individual counseling sessions (all of them had over 5 years of experience working in psychiatry). The health psychologists were trained in several steps by an experienced MI trainer (the first author). The training consisted of two weeks training sessions that focused on didactic and experimental learning. Goals of the training sessions were to convey the sprit, processes and skills of the MI to help the health psychologists to conduct the MI with competency. The first week focused on introduction to MI, application of MI and clinical training. The second week focused on advanced clinical training, supervisor training and training for trainers. The content of the MI sessions was selected based on Motivational Interviewing Training New Trainers Manual (http://www.motivationalinterview.org).

The facilitators used the following MI techniques to help the patients to take their medication regularly: Open-ended questions, rolling with resistance, setting agenda and eliciting self-motivational statements, change talk and affirmations.

The first session was designed to prepare the patient for the MI. The facilitator introduced themselves to the patients and assured them that the conservations would be kept private. Afterward, the facilitator encouraged the patients to discuss and list any concerns that may interfere with their willingness and motivation to receive psychiatric treatment and take medication by asking some basic questions (such as "What do you call your problem?", "What do you think has caused your problem?", and "What do you fear most about your illness?"). Facilitators also provided information on the medication that patients should take (dose and timing, adverse effects, contradictions, and treatment process).

During the second session, the facilitators tried to persuade the patients to commit to change and adhere to the treatment. Open-ended questions (e.g., "*So how have things gone this week?" and "How have you been feeling?"*) were used to assess new stressors and changes in the environment that were likely to affect the patients. The facilitators also inquired about patients' adherence and the response to the medication and helped each patient to weigh up the perceived costs and benefits of taking medication (e.g., *"What do you see as the positive and negative consequences of taking medication?"*). The patient's readiness to change was rated on a scale from 1 (I'm not willing to change) to 10 (I will do anything that I need to change). The importance of taking medicine regularly was also raised by the counselors and was rated by the patients on a scale from 0 (least important) to 10 (most important). These questions were followed up by open-ended questions that invited patients to further elaborate on their choices (e.g., "*Why did you choose a (current number) instead of a (lower number)?*", "*What would need to*

happen to make it a (higher number)?"). The patients were also encouraged to think about what it would be like to make the change by imagining future situations; (e.g., *"If you were successful in taking medicine regularly, how would things be different?"* Finally, the facilitators measured and discussed patients' confidence in their ability to change by asking questions such as "*On a scale from 0 to 10, where 10 is the most confident and 0 is the least, what number would you give for how confident you are that you could taking medicine regularly?*"

The third session addressed potential obstacles to MA. The facilitator helped the patients to review progress, and sought to renew and reinforce patients' motivation. Patients were helped to identify obstacles that might prevent them from taking medication, to identify strategies to overcome obstacles that arise, and to build self-efficacy. In addition, patients were invited to set goals and make plans to support desired changes. Worksheets were given to the patients that encouraged them to identify things that they would need to do to achieve a given goal. Furthermore, the facilitators encouraged the patients to create an action plan by specifying where, when and how they would take their medication. Patients were also asked to anticipate situations in which it might be difficult to take medication and were encouraged to identify strategies to overcome these barriers (coping planning).

In addition to the MI sessions for the patients, a single MI session was conducted for the family members of the patients in the EXP group. The same facilitators contacted each family member by telephone and invited them to attend a single session. At the beginning of the session, the family members were encouraged to express their feelings about patients' medications and their role in supporting patients to take their medication regularly was discussed. Barriers and facilitators to behavior change were also explored and the facilitators helped the family member to identify the pros and cons

of helping the patients take their medication regularly. The family member rated the patients' level of commitment and likelihood of success on a 0-10 scale. Family members were encouraged to imagine the patients in the future with and without change. Family members were asked to help their patients to use reminders (such as phone alarm or sticky notes) to improve their MA.