Title: Enhancing adherence and outcomes in bipolar disorder with Abilify Maintena + a targeted behavioral approach to promote sustained adherence and behavioral change

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Version Date: December 18, 2017

Background:

Poor adherence with medication in bipolar disorder (BD) is associated with relapse, high use of health resources, poor outcomes, and suicide. The proposed project will build upon the recent availability of long-acting aripiprazole (Abilify Maintena) combined with manualized adherence support to meet the specific needs of poorly adherent BD patients. An innovative and clinically important "deliverable" of the proposal will be a practical treatment approach that can be scaled-up widely in routine practice settings.

Long-acting injectable antipsychotic (LAI) in BD: Oral Abilify (aripiprazole) is effective in the treatment of patients with BD when prescribed as an acute anti-manic agent and for the maintenance treatment of bipolar disorder. Abilify Maintena is an intramuscular (IM) depot formulation of oral aripiprazole (Abilify). It is a sterile lyophilized powder that, when reconstituted with sterile water for injection, forms an injectable suspension that can be administered monthly. After an initial injection of Abilify Maintena, along with an overlapping 14-day dosing of oral antipsychotic treatment, subsequent injections of Abilify Maintena provide uninterrupted medication coverage for 30 days at a time. Abilify Maintena appears to be as effective as standard oral Abilify and may maximize patient adherence. Recent clinical trials suggest that Abilify Maintena is effective for the treatment of patients with BD.

Customized Adherence Enhancement (CAE) is a brief behavioral intervention that improves adherence approximately 30% more than an educational control in adults with BD. The CAE program is a brief, practical intervention consisting of a series of up to four psychosocial treatment modules based upon an adult's unique adherence barriers: 1) Psychoeducation on BD Medications; 2) Communication with Providers; 3) Strategies to Enhance Medication Routines; and 4) Targeting Substance Use Problems with Modified Motivational Enhancement Therapy. These CAE modules are derived from existing evidence-based approaches for patients with BD (Bauer 2004, Bauer 2006a, Bauer 2006b, Frank 2005, Sajatovic 2005, Ziedonis 2005). Each CAE module can be combined with other CAE modules. The material can be delivered in approximately 6 in-person sessions.

These investigators conducted 2 pilot trials of CAE that were nearly identical in design. The first trial was an NIMH-funded 6-month pilot evaluating the feasibility/acceptability and preliminary efficacy of CAE in 43 poorly adherent BD adults (Sajatovic 2012a) and the second trial was an industry-funded 3-month trial in 43 poorly adherent BD adults(Sajatovic 2012b). In both trials, the primary outcome was adherence evaluated with the Tablet Routines Questionnaire (TRQ; Peet 1991, Scott 2002). Pooled results indicated mean baseline non-adherence (proportion of missed medication) was 40.2% (SD 31.6%) within the past week and 42.8% (SD 28.1%) missed medication within the past month. At 3 months, mean missed medication decreased to 18.5% (SD 31.9) for the past week, and 15.8% (SD 26.1%) for the past month. At 6-month follow-up, mean missed tablets was 25.2% (SD 36.2%) for the past week and 21.3% (SD 29.1%) for the past month.

A 6-month, prospective, randomized controlled trial (RCT) of CAE vs. an educational control is being conducted in 184 poorly adherent adults with BD. To enhance generalizability, CAE is delivered by social workers. Interim RCT outcomes (CAE N=24, EDU N=26) show that CAE is associated with improved adherence as measured by the Tablet Routines Questionnaire (TRQ mean change=46.0, SD=38.7) compared to an educational control (EDU) (TRQ mean change=17.3, SD=40.3, p=.017). Six-month MEMS adherence change was also greater with CAE (mean change 45.7, SD 40.6) compared to EDU (mean change 15.9 (SD 39.9), p=.015. Effect sizes for CAE in both TRQ and MEMS are approximately 0.75, comparing favorably with effect size for response to BD medications.

Combining LAI + CAE dramatically improves adherence, symptoms and functional outcomes in people with schizophrenia and schizoaffective disorder: These investigators tested a combined LAI + CAE approach (CAE-L) in 2 preliminary studies. CAE-L Study 1 (Sajatovic 2013) enrolled 30 homeless or recently homeless individuals with schizoaffective or schizophrenia. The LAI used was haloperidol decanoate. Primary outcomes were TRQ and housing status. Secondary outcomes included psychiatric symptoms and functional status. Mean sample age was 41.8 years with a high proportion of minorities and single/never married individuals. CAE-L was associated with substantial improvement in concomitant orally prescribed medication, which changed from missing 46% of prescribed medication at study enrollment to only 10% of prescribed medication at study end. Mean proportion of time in sub-optimal housing went from 56% in the 6 months prior to study enrollment to 41 % in the first 3 months of the study and 14% in the last 3 months of the study. There were also significant improvements in psychiatric symptoms and functional status.

In CAE-L Study 2 (Sajatovic 2016), CAE-L was delivered by social workers and used the LAI paliperidone palmitate. This 6-month prospective, uncontrolled trial of CAE-L in 30 recently homeless individuals with schizophrenia or schizoaffective disorder assessed medication adherence using the TRQ and injection frequency. Psychiatric symptoms were measured with the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS) and global psychopathology. Standardized measures of extrapyramidal symptoms included the Simpson Angus Scale (SAS), the Barnes Akathisia Scale BAS), and the Extrapyramidal Symptoms Scale-Abbreviated version (ESRS). Social functioning was assessed via the Social and Occupational Functioning Assessment Scale (SOFAS). Mean age of the sample was 43.6 years, mainly minorities, single/never married with a mean of 11.55 years of education. Baseline rate of substance abuse within the past year was 40.0%. Four individuals (13.3%) terminated the study prematurely. CAE + LAI was associated with improved adherence as measured by the TRQ (p=.02). There were significant improvements in PANSS (p <.01), BPRS (p<.001), CGI (p =.003) and SOFAS (p=.005). There were no significant mean changes on SAS, BAS, ESRS-A. The CAE-L studies combined dataset (Table 1)(Sajatovic M 2016) shows changes in medication adherence, psychiatric symptoms, global psychopathology and social functioning. Adherence with regular LAI injections was excellent, with > 90% receiving injections within 1 week of regularly scheduled treatment.

Table 1: Combined data of CAE-L for 60 poorly adherent patients with schizoaffective disorder/schizophrenia

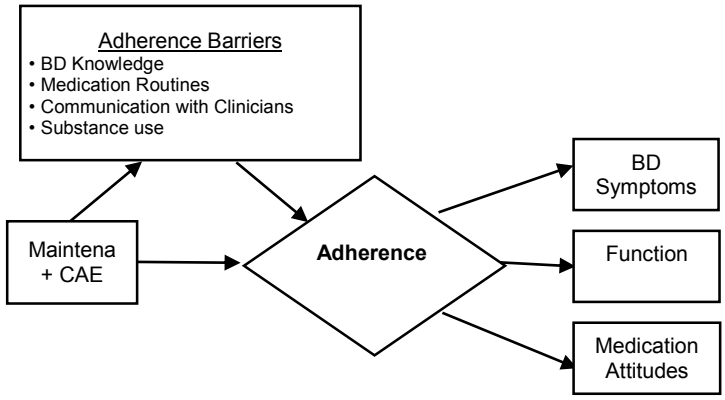
Variable	Screen	Baseline	Wk 13	Wk 25	N	Statistic
TRQ Mean						
Past Week	50.4% (32.4)	26.7% (29.3)	16.8% (29.5)	17.1% (30.6)	26	**.001**
Past Month	45.2% (33.6)	32.5% (30.4)	16.2% (24.9)	13.8% (23.2)	25	**.002**
Injection Frequency	-	-	86.1 (32.8)	90.5 (30.1)	50	.060
BPRS Mean	-	44.1 (8.3)	33.9 (7.9)	30.8 (8.3)	41	**< .001**
PANSS Mean						
Positive Symptoms Scale	-	16.7 (6.3)	-	12.4 (5.8)	36	**.001**
Negative Symptoms Scale	-	28.5 (10.9)	-	20.8 (7.9)	35	**<.001**
Composite Scale (Pos - Neg)	-	14.9 (10.3)	-	7.8 (8.2)	36	**<.001**
General Psychopathology Scale	-	19.9 (18.9)	-	9.8 (14.1)	36	**<.001**
CGI Severity Mean	-	4.6 (0.9)	3.4 (0.7)	3.1 (0.8)	38	**<.001**
SOFAS Mean	-	51.1 (8.1)	-	61.3 (9.7)	40	**<.001**

In summary, LAI can maximize medication adherence, while CAE addresses individual barriers to sustained adherence and behavioral change. Combining LAI + CAE improves adherence, symptoms and functioning in high-risk people with primary psychotic disorders. The proposed project will test the efficacy of combining Abilify Maintena with CAE to help improve outcomes in poorly adherent patients with BD. Pilot data suggest that adherence with concomitantly prescribed psychotropic drugs improves with LAI + CAE. The findings have particular relevance to BD because many BD patients are on concomitant oral psychotropic drugs in addition to antipsychotic. Thus, it is expected that combining CAE with LAI will lead to a "halo effect" in that these BD patients will engage in their own care more broadly.

Methods:

Rationale for combined drug + behavioral approach: In spite of the advantages of LAI in promoting adherence and treating BD symptoms, simply switching individuals who are poorly adherence to LAI is often not enough to sustain long-term behavioral change. Additionally, many people with BD are on multiple psychotropic medications, some of which are not available in LAI formulations. Adherence is a multi-component process that involves having 1) knowledge of what is needed to manage a medical condition, 2) organizational resources to put a self-management plan into action, 3) ability to communicate with health care professionals to effectively manage a care plan, and 4) understanding of the impact of substance use on adherence. Problems with any of these components can impede adherence, and when multiple barriers are present, adherence is particularly difficult. Each additional barrier increases the likelihood of poor adherence by 30% (Zeber 2011). While addressing adherence barriers is challenging, the gains in outcomes may be substantial and improved adherence behavior is associated with reduced psychiatric symptom burden and improved functioning(Levin 2014, Sajatovic 2013, Sajatovic 2012a, Sajatovic 2012b).

Figure 1. Targeted mechanism of action of a customized adherence enhancement approach (CAE-L) in BD



An important limitation of the CAE-L pilots is that they excluded individuals with BD. The pilot studies combined LAI + CAE data suggested that patients with schizoaffective disorder (N=44) did just as well as those with schizophrenia (N=16) with respect to adherence, symptom and functional outcomes (Levin et al., 2017). Combining Maintena with a practical method of adherence support has potential to enhance uptake and optimize enduring adherence to medication in patients with BD.

Project Design:

Overview: 6-month, prospective, trial testing the effects of Maintena augmented with CAE in 30 poorly adherence patients with BD. After a 2-month study start-up period, patients will be enrolled over a 16 month enrollment period (months 2-18). The targeted enrollment of approximately 2 participants/month is reasonable given previous recruitment with the CAE + LAI pilots. Primary outcomes will be change from baseline in adherence as identified by the Tablet Routines Questionnaire (TRQ) and injection frequency at the 6-month time-point. We will also evaluate changes in secondary outcomes, including BD symptoms (BPRS), depressive and global psychopathology symptoms, functional status, and adherence attitudes. Additional exploratory assessments will include health resource use, adherence barriers, substance use and neurocognition. Outcome measures will be assessed at Screening, Baseline, and Weeks 4- 24 as noted in Table 2/Study Schedule of Events. Because the study design will be nearly identical to the 2 previously conducted CAE + LAI pilots, it will be possible to compare primary and secondary outcomes of this study of individuals with BD to individuals with schizophrenia/schizoaffective disorder. The study will be operationalized in 4 specific Aims:

Aim 1: Test whether combined Maintena + CAE (Maintena +) is associated with improved treatment adherence
Hypothesis 1: At 6-month follow-up, poorly adherent BD patients receiving Maintena + will have significant improvement in medication adherence as measured by the TRQ.
Hypothesis 2: At 6-month follow-up we also expect that mean LAI adherence as measured by injection frequency will meet or exceed 80%. The 80% threshold is widely viewed in the treatment adherence literature as an "acceptable" degree of adherence.

Aim 2: Test whether Maintena + is associated with reduction in BD symptoms, improved functioning and better treatment attitudes
Hypothesis 3: Maintena + will be associated with significant reduction in symptoms, improved functioning and better treatment attitudes.

Aim 3: Compare how individuals with BD participating in a care approach that combines LAI with a brief behavioral approach that targets adherence enhancement respond on adherence, symptom and functional outcomes in comparison to individuals with schizophrenia/schizoaffective disorder. This comparison will use outcomes from the current study vs. historical data from recently conducted trials in schizophrenia/schizoaffective disorder. Corresponding effect sizes will be computed. Based on past data comparing individuals with schizophrenia vs. those with schizoaffective disorder, we expect that BD patients will do at least as well, and possibly better than individuals with primary psychotic disorders.

Aim 4: Investigate whether improved adherence behaviors will be associated with reductions in treatment adherence barriers.
We expect that improved BD knowledge, communication with clinicians, medication routines and reduction in substance use will all be associated with improved adherence. Exploratory analysis will investigate mechanistic effect of Maintena + by evaluating whether change in BD knowledge, communication with clinicians, medication routines and substance use is related to adherence change. Additional exploratory measures will evaluate health resource use, substance use/abuse and neurocognition.

Study Population:
The study will enroll 30 individuals age 18 and over with Type 1 or Type 2 BD. Patients will be recruited from inpatient, ambulatory services and from the community by a variety of methods:

1. Study staff will inform the University Hospitals of Cleveland Medical Center (UHCMC) clinical psychiatry providers about the study.
2. Study staff will also present information about the study to the staff at local Community Mental Health Clinics (CMHCs) and other organizations serving persons with mental illness. After presenting the study in these group and individual settings, the study staff will maintain regular contact with staff at these organizations to inquire about new referrals.
3. IRB-approved recruitment fliers will be posted and distributed with permission of staff at CMHCs and other organizations serving persons with mental illness.
4. Recruitment will be done by oral request to patients coming for regularly scheduled clinic visits at UHCMC or area CMHCs. Requests for participation may be initiated by a clinic staff member, by a research associate on site, or in some cases may be initiated by patients themselves.
5. Patients with BD will be identified from the UHCMC electronic medical record and using an IRB-approved process, be invited to participate in study screening.
6. Patients may also be recruited under the MHERP/NBOC Prescreen protocol.

All individuals with BD who are referred will be considered for possible inclusion in the study. A Screening Form for each patient will be completed regardless of whether the patient is ultimately enrolled. The form will detail reasons for exclusion, allowing an estimate of sample generalizability. Patients recruited in response to an IRB-approved recruitment method may be prescreened under the IRB-approved protocol, "Prescreening and Recruitment for the Mental Health Effectiveness Research Program and Neurological and Behavioral Outcomes Center" (MHERP/NBOC Prescreen) [IRB # 03-10-09].

The study PI (Dr. Sajatovic, Professor of Psychiatry at CWRU and UHCMC) will oversee and be responsible for all aspects of the study including study regulatory matters, human subjects requirements, study implementation, study staff supervision, and data collection, analysis and reporting. Study Co-investigators will assist the study PI in study referral, clinical and safety monitoring, training and oversight of interventionists, and participant retention. The PI has successfully conducted multiple treatment adherence studies over the last decade and has an extensive track-record of robust recruitment of non-adherent patients with BD and other serious mental illnesses. Diagnosis will be confirmed with a standardized brief interview commonly utilized in clinical trials, the Mini International Neuropsychiatric Inventory (MINI). In order to facilitate a relative comparison of BD patient response to outcomes in this study vs. recently completed pilot trials, we will deliberately recruit individuals with similar study entry level symptom severity. In the proposal trial, study entry Brief Psychiatric Symptom Rating Scale (BPRS) scores will not be below 1 standard deviation of the mean BPRS in pilot work.

Inclusion Criteria:

1. Individuals age 18 and older with BD Type 1 or 2 as confirmed by the Mini International Psychiatric Inventory (MINI).

2. Known to have medication treatment adherence problems as identified by the Treatment Routines Questionnaire (TRQ, 20% or more missed medications in past week or past month)
3. Screening BPRS score of ≥ 36
4. Ability to be rated on psychiatric rating scales.
5. Willingness to take LAI
6. Currently in treatment or scheduled to receive treatment at a Community Mental Health Clinic (CMHC) or other clinical setting able to provide mental health care during and after study participation
7. Able to provide written, informed consent to study participation.

Exclusion Criteria:

1. Individuals on LAI immediately prior to study enrollment.
2. Individuals with known intolerance or resistance to either oral aripiprazole or LAI formulation of aripiprazole
3. Prior or current treatment with clozapine
4. Medical condition or illness, which in the opinion of the research psychiatrist, would interfere with the patient's ability to participate in the trial
5. Physical dependence on substances (alcohol or illicit drugs) likely to lead to withdrawal reaction during the course of the study in the clinical opinion of the treated research psychiatrist
6. Immediate risk of harm to self or others
7. Female who is currently pregnant or breastfeeding

Study Medication: Medication dosing will follow recommendations in the Maintena package insert. For patients who have never received aripiprazole, there will be a brief oral tolerance testing (OTT) of up to 14 days. Individuals who tolerate OTT will then receive 400 mg of Maintena administered IM in the gluteal or deltoid location, and oral Abilify will continue for an additional 14 days, after which oral medication will be discontinued. After the initial IM injection, individuals will continue to receive injections of Maintena every month for a total of 6 months. The standard dosage of 400 mg IM will be administered in this maintenance treatment phase although clinicians may administer a lower dosage of 300 mg IM depending on clinical response.

Concomitant Medications As it is known that multi-drug maintenance treatment is the rule rather than the exception in BD, and in order to increase generalizability of study findings, patients will be permitted to continue other psychotropic maintenance treatments. Maintenance treatments are defined as traditional mood stabilizing drugs (such as lithium, valproate or lamotrigine), or antidepressants that have been continued for at least one month at a stable dosage. Dosing on other concomitant treatments is required to remain unchanged for the duration of the study. Medications for side effects (for example, benztropine) may be given at the discretion of the treating psychiatrist. Hypnotic drugs for insomnia/sleep that have been prescribed for at least 30 days may continue to be administered daily (for example zolpidem) at the same dosage.

CAE: The CAE intervention will be modeled and delivered using procedures used in the CAE + LAI pilots. CAE will be delivered by a trained social worker to optimize generalizability. CAE session will be delivered on the same day (either immediately before or immediately after Maintena injection). Supervision will be conducted with a PhD psychologist who helped develop CAE and training will be reinforced as needed.

Measures and Schedule of Events: Table 2 shows the assessment measures, timeline the measures are given, and other specific procedures in the study. Demographic and clinical variables measured at baseline will include age, gender, race/ethnicity, living situation, cumulative medical burden and socioeconomic status at baseline. As in 2 previous successful studies using the medication + adherence support approach in high-risk SMI (Sajatovic 2012a, Sajatovic 2012b) the primary outcome measure will be adherence as assessed via the Tablet Routines Questionnaire (TRQ)

Adherence: A number of investigators have defined "good" adherence in serious mental illness as missing no more than 20% of medication (Gilmer 2004, Valenstein 2004). In previous studies, we demonstrated that this cut-off is sufficient to detect adherence change over time with CAE (Levin 2014, Velligan 2010). Adherence to Maintena will be assessed using the same injection frequency benchmarks used in the previous CAE-L studies (injection is counted as "adherent" if administered within 7 days of when it is scheduled to be administered).

Barriers assessed include BD knowledge, communication with clinicians, medication routines, and substance use.

Other measures:
Symptoms: Symptoms of BD will be addressed using the *Brief Psychiatric Rating Scale (BPRS)* developed by Overall and colleagues (Overall 1962), the Young Mania Rating Scale (Young 1978) and the Montgomery Asberg Rating Scale (Montgomery 1979), Global psychopathology will be measured with the *Clinical Global Impressions* , a widely used scale which evaluates illness severity on a 1 to 7 point continuum. Severity of illness ratings on the CGI have reported reliability scores ranging from 0.41-0.66.

Functioning: Life and Work Functional status will be evaluated using the *Social and Occupational Functioning Scale* (Morosini 2000) and the GAF. The GAF is a 100-point single-item scale which measures global functioning of psychiatric patients and is widely utilized in clinical studies involving Seriously Mentally Ill patients (Jones 1995).

Adherence Attitudes:
The Drug Attitude Inventory () is used to measure attitudes towards medication among individuals with serious mental illness (Awad 1993), and is known to be relatively unaffected by psychiatric symptom severity (Sajatovic 2002). The DAI was originally developed to assess the attitudes and subjective experience of patients with schizophrenia being treated with antipsychotic medications and has also been widely utilized with other seriously mentally ill populations receiving psychotropic medication (Sajatovic 2003). The 10-item version of the scale will be utilized (Awad 1993).

Attitude towards Medication Questionnaire (AMSQ): A modification of the Lithium Attitudes Questionnaire, the AMSQ evaluates an individual's attitudes towards psychiatric medication. The AMSQ comprises 19 items grouped into 7 subscales: general opposition to prophylaxis (4 items), denial of therapeutic effectiveness (2 items), fear of side effects (2 items), difficulty with medication routines (4 items), denial of illness severity (3 items), negative attitudes toward drugs in general (3 items), and lack of information about psychiatric medication (1 item). Higher scores on each subscale represent more negative attitudes toward mood stabilizers.

Adherence Barriers:
BD Knowledge: Oxford Bipolar Knowledge Questionnaires 40-item self-report questionnaire used to assess knowledge of BD management on a 3-point Likert scale from agree to disagree (Bilderbeck 2016).

Medication Routines: Routines will be assessed using The Self-Report Habit Index (SRHI), a 12-item self-report measure of habit strength and will be administered regarding the habit of taking medication (Verplanken 2003).

Communication with Providers: Provider communication will be assessed the Communication Styles Scale, a patient rated measure of the impact of physician communication style on medication beliefs and adherence behavior in depressed patients(Bultman 2000).

Motivation to Reduce Substance Use: Motivation to reduce the use of substances will be assessed using the 19 item Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES 8A) (Miller WR 1996).

Neurocognition: Trail Making Test Parts A and B (Howieson 2004) and Animal Fluency Test (Lezak 2012) will be administered to assess for executive functioning and semantic verbal fluency, respectively.

Health Resource Use: Resources that are typically utilized by the most severely ill individuals with BD include emergency care and hospitalization. Resource use in the 6-month period prior to study enrollment and in the 6-month study period will be evaluated.

Alcohol and Substance Use: Alcohol use will be evaluated using The Alcohol Use Disorders Identification Test – Self-Report Version (AUDIT), a 10-item measure used to screen for excessive alcohol use developed by the World Health Organization (WHO)(Babor 2001, Saunders 1993). Drug use will be evaluated using the Drug

Abuse Screening Test (DAST-10), a 10-item abbreviated version of the original 28-item DAST created to assess drug-related problems in the past year (Babor 2001, Maisto 2000).

Satisfaction with treatment: Treatment acceptability and satisfaction will be assessed with a Likert Scale.

Safety Evaluations:
Safety evaluations will include baseline and Week 24/End-of-study basic laboratory evaluations (comprehensive metabolic panel, lipid profile, CBC with differential) and pregnancy testing for women. EKG will be conducted at baseline, week 4 and Week 24/End-of-study. Patient vital signs and weight will be collected at each study visit (baseline/V1, V2, V3, V4, V5, V6, V7, V8). Standardized measures of involuntary movements/ extrapyramidal symptoms will be assessed with the Simpson Angus Scale (SAS), the Barnes Akathisia Scale (BAS), the Abnormal Involuntary Movement Scale (AIMS) and the Extrapyramidal Symptoms Scale-Abbreviated version (ESRS-A). Finally, reported side effects will also be evaluated at each study visit using a form derived from the previous CAE-L studies.

Table 2: Measures and Study Schedule of Events

Visit	Screen	BL/ V1	V2	V3	V4	V5	V6	V7
Timing┼	−14 d to −1d	0 W	4W	8W	12W	16W	20W	24W
Informed consent	X							
Inclusion/Exclusion	X							
Adherence Behavior: TRQ LAI Injection Frequency*	X	X	X	X	X	X	X	X
Non-psychotropic drug TRQ	X				X			X
MINI	X							
CAE module allocation and assessment of Adherence barriers	X							X
Physician Exam and interview	X							X
Demographics, medical burden	X							
Laboratory testing	X				X			X
EKG	X		X					X
Adherence Attitudes: DAI, AMSQ		X			X			X
Symptoms: BPRS, YMRS, MADRS, CGI	X†	X			X			X
Functioning: SOFAS, GAF		X						X
Health resource use		X						X
Alcohol/Substance Use: AUDIT, DAST-10		X			X			X
Trails A & B, Animal Fluency	X							X
Weight and vitals		X	X	X	X	X	X	X
Reported Side Effects		X	X	X	X	X	X	X
Extrapyramidal symptoms: AIMS**, SAS, BAS, ESRS-A	X	X	X	X	X	X	X	X
Patient Satisfaction					X			X
Research Clinician assessment		X	X	X	X	X	X	X
CAE sessions		X	X	X	X	X	X	X
Oral aripiprazole Dispensing***	X	X						
LAI Injection		X	X	X	X	X	X	X

┼Timing of visits is approximate.
* LAI Injection frequency will be calculated at weeks 12 & 24.
** AIMS will only be administered at BL and W24/Term
*** Dispensing of oral medication is patient specific and may include a 14-day oral tolerability test prior to first LAI injection, or dispensing of anti-side effect medications.
† BRPS will be the only symptom evaluated at screen

Laboratory testing includes: Comprehensive metabolic panel, CBC with differential, Thyroid function. Pre-menopausal females will require serum pregnancy testing. Women of childbearing potential must be using medically accepted methods of birth control. Week 12 lab testing will only include serum pregnancy testing for pre-menopausal females. Pregnancy testing may also be done at any time point if a woman feels she may be pregnant.

Serious Adverse Event Reporting

1. Serious adverse events (SAEs) and other safety information will be collected and reported to the relevant government authority in accordance with the current Code of Federal Regulations
2. Safety Information is defined as, any information from any source containing information such as:
   - Adverse event or suspicion thereof
   - Lack of efficacy
   - Overdose/incorrect dosage (accidental or intentional)
   - Abuse/misuse (e.g., patients sharing medication) even without resulting adverse reaction
   - Accidental exposure (e.g., child takes parent's medication)
   - Medication error
   - Withdrawal reactions
   - Disease progression/exacerbation of existing disease
   - Drug-drug/Drug-food interaction
   - Reports of unexpected benefit
   - Exposure to drug during pregnancy, where the embryo or fetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure).
   - Exposure to drug during lactation (including uneventful)
   - Suspected counterfeit product
   - Suspected transfer of infectious disease/agent by the medicinal product concerned.
   - Product complaint report (any deficiencies related to the identity, quality, labeling, durability, reliability, efficacy, performance of a medicinal product, suspected counterfeit product)
   - Pediatric use (if not an approved use)
   - Occupational exposure
   - Off-label use (if not part of the study design)
3. SAEs and safety information will be collected from first use of an Otsuka product until 28 days after discontinuation.

Data Management & Analyses: Study data will be collected and managed using REDCap(Harris 2009), a secure, web-based application designed to support data capture for research studies.

Sample Size and Power: We propose to enroll 30 individuals with BD who receive Maintena +. Based on our prior studies (Sajatovic 2012a, Sajatovic 2012b), we conservatively assume 20% of participants will discontinue study participation during the 24 week study period and that the effect size of CAE-L will be similar to that of CAE-L in prior studies (effect size *d*=.60). Type I error level of 0.05 will be adopted for all tests.

The primary outcomes measure will be change in adherence behavior and the mean LAI injection frequency at 6-months. Adherence rates will be calculated for TRQ in the following manner: the number of days with a missed dose will be divided by the number of days in the time period and then multiplied by 100. Adherence rates will be calculated for both the week and the month prior to assessment visit and for the study period. Given a sample size of 30 subjects with 20% attrition and two-sided Type I error of 0.05, for paired t-tests we will have power of 0.80 for effect sizes of at least 0.597. For correlations, power of 0.80 is achieved for a two-sided test of correlation being zero when the magnitude of correlation is at least 0.51. Hence, there is sufficient power to detect moderate level mean differences and correlation values. For the assessment of mean injection frequency, suppose 6 prescribed injections in 6 months, with a standard deviation of 1.2 (20% of prescribed injections). Then, if a sample mean of 5.28 or higher is observed (88%), a 95% two-sided confidence interval will not contain 4.8, the 80% threshold, This would provide evidence that the percentage of injection frequency is higher than 80%. Note that adherence levels of 80% or higher are widely considered to be "acceptable" adherence in the research literature. The mean LAI injection frequency in our previous pilot work involving LAI + CAE in homeless patients with schizophrenia exceeded 90% of prescribed injections at 6-month follow-up. We thus expect to statistically establish that the mean LAI injection frequency in this bipolar sample who are not homeless is above the 80% threshold.

Data analyses will be performed using the Statistical Analysis System (SAS) (SAS Institute, Cary, NC, 2002).. For Aim 1, change in TRQ from baseline to 24 weeks will be assessed with a paired t-test or Wilcoxon signed rank test. For mean LAI injection frequency, we will construct 95% confidence intervals. Exploratory longitudinal

models of adherence will be considered as well. We may represent adherence as a binary outcome, indicating whether or not an adherence threshold has been met (e.g., 80% adherent), particularly if adherence levels are highly skewed. Exploratory logistic regression through generalized estimating equations (GEE) or generalized linear mixed models for binary outcomes will thus be considered for assessing effects of time. Time may be modeled with a slope parameter or treated as a categorical variable. Age, race, duration of illness, and/or gender will be considered as possible covariates. In addition, we will compare corresponding TRQ and SimpleMed pillbox adherence levels. Correlation between the adherence measures will be estimated and Bland-Altman plots will be generated (Altman 1983).

Aim 2 will evaluate change from baseline to 24 weeks in TRQ, psychiatric symptoms (BPRS, MADRS, YMRS, CGI) in a similar manner as in Aim 1. For Aim 3, change in the outcome variables and other secondary measures in the proposed study vs. historical controls (the previously conducted CAE + LAI pilots) will be compared through effect sizes. In Aim 4, adherence barriers will be evaluated as well. Mean change in symptom rating scales, functional level and medication attitudes will be estimated from baseline to the various follow up periods. We will explore whether reductions in adherence barriers (e.g., BD knowledge, medication routines, communication, and substance) will be associated with changes in adherence behavior. Correlations between respective changes in barriers and adherence levels will be computed. In a similar manner, we will also examine whether improvements in adherence behaviors correlate with improvements in symptoms, functioning, and medication attitudes.

Study reporting/deliverables: Reporting on study outcomes will be focused on rapidly available and impactful findings. As the study does not require blinding, it is expected that interim results can be used for new research abstract proposals that can be submitted even while the study is ongoing. It is expected that study results will be presented at a minimum of 2-3 suitable scientific venues including (but not limited to):

- American College of Neuropsychopharmacology (ACNP)
- American Psychiatric Association (APA)
- International Society for Bipolar Disorders (ISBD)

The study findings will also be prepared in manuscript format suitable for submission to an appropriate peer-reviewed scientific journal with a readership that can use study findings to inform clinical practice and future research. Manuscripts given high consideration will include Bipolar Disorders or other publications with a similarly-oriented audience target.

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