Protocol Title: ***Improving Medication Adherence in Hypertensive Individuals with Bipolar Disorder*** **(iTAB-CV) - Phase 2**

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Background and Rationale:

Individuals with bipolar disorder (BD) are prone to chronic medical conditions leading to mortality rates two to three times that of the general population and cardiovascular (CV) disease accounts for more than two-thirds of these deaths (Osby, Brandt, Correia, Ekbom, & Sparen, 2001; Ramsey et al., 2013). While there are multiple factors contributing to the profound morbidity and premature mortality in people with BD, there is an immediate and correctable course of action to reduce CV risk in this population. Poor adherence to antihypertensives, estimated to occur in 50-80% of patients (Costa, 1996; Cramer, Benedict, Muszbek, Keskinaslan, & Khan, 2008), significantly increases the risk of acute CV events but is a modifiable factor that when treated, can make a profound positive impact on health outcomes. Given the dramatic decrease in CV events since the introduction of antihypertensives in the general populace (Corrao et al., 2011), it is reasonable to expect that similar gains could be achieved by optimizing adherence to antihypertensives in persons with BD.

Current reviews indicate insufficient evidence for effective interventions that improve adherence to antihypertensives (Nieuwlaat et al., 2014; Viswanathan et al., 2012). Similarly, while there is ample literature documenting the enormity and negative effects of psychotropic medication non-adherence in BD (Hong, Reed, Novick, Haro, & Aguado, 2011), there are a lack of effective interventions to enhance psychotropic medication adherence and improve clinical outcomes (Nieuwlaat et al., 2014). Given that addressing adherence to both psychotropic and non-psychotropic medications simultaneously is likely to be both more effective and sustainable, we propose developing a practical intervention which addresses both types of medication adherence.

The Attitude-Social Influence-Efficacy (ASE) model (De Vries & Mudde, 1998) frames adherence to medication as deriving from attitudes (A), social influence (S), and self-efficacy (E). However, adherence also requires intact prospective memory, the ability to remember to do a behavior in the future, which tends to be impaired in those with BD (Bogner, de Vries, O'Donnell, & Morales, 2013; Lee et al., 2010; Zogg, Woods, Sauceda, Wiebe, & Simoni, 2012). Given this deficit, even when an individual has the intention to take medication, they lack the planning or organizational abilities to do so consistently (Zogg et al., 2012). Thus, in order to change and sustain medication adherence in this and similar populations, one must address both ASE and prospective memory. This m-Health intervention primes habit formation by targeting behavioral intention using customized psychoeducational and motivational texts with social reference followed by contextual cues, reminders, and immediate positive reinforcement, to create a strong and automatic habit of taking medication which will be sustainable despite variability over time in behavioral intent.

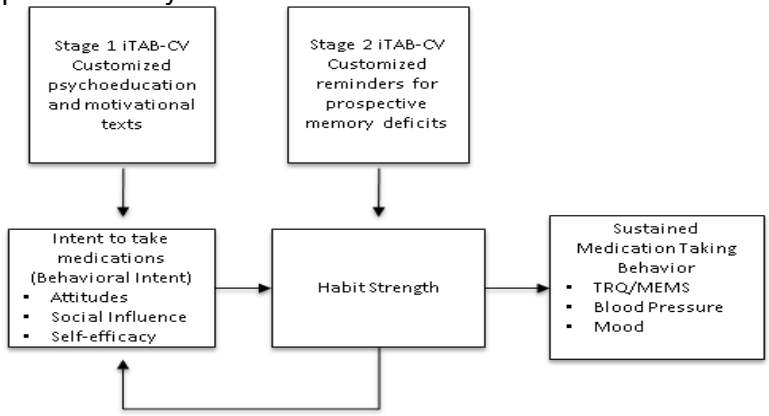

Figure 1: Diagram of expanded ASE model

This study aims to test the feasibility, acceptability and effectiveness of a customized m-Health texting intervention built on the Individualized Texting for Adherence Building (iTAB) platform on antihypertensive adherence and systolic blood pressure in hypertensive persons with BD. This practical, customized intervention, intended to improve adherence to antihypertensives and BD medication among high risk individuals, will be suitable for implementation in either primary care or mental health settings and may reverse the unacceptably high morbidity and mortality in this population.

This study has one specific aim:

Specific Aim 1: To test the acceptability, feasibility and effectiveness of iTAB-CV to improve adherence to antihypertensives based on self-reported Tablets Routine Questionnaire (TRQ) and a medication event monitoring system (eCAP).

Hypothesis 1: iTAB-CV will improve adherence to antihypertensives in non-adherent persons with BD and HTN.
Hypothesis 2: Participants will respond to at least 75% of text messages.
Hypothesis 3: At least 75% of participants will find iTAB-CV acceptable based on exit interviews.

Exploratory Aims: *Secondary outcomes* Change in systolic BP, change in TRQ for BD medications, change in attitudes and self-efficacy for adherence, health status, healthcare utilization (number of hospitalizations and ER admissions), and psychiatric symptoms. Habit strength, prospective memory and mood will be evaluated as possible variables of interest.

Methods:
Overview:
This study will test an adherence intervention (iTAB-CV) delivered via interactive text messaging which first targets behavioral intent and then adds cues/reminders and reinforcement to form the habit of taking antihypertensives in non-adherent individuals with BD. Thirty eight individuals with BD and HTN being treated with evidence-based antihypertensive agents and mood stabilizing or antipsychotic medications who are non-adherent with their HTN medicine will be enrolled. This phase uses a prospective cohort design with participants serving as their own control. We will test the iTAB-CV intervention quantitatively for feasibility and acceptability as well as for efficacy in increasing adherence to antihypertensives, decreasing systolic blood pressure, and increasing adherence to BD medication.

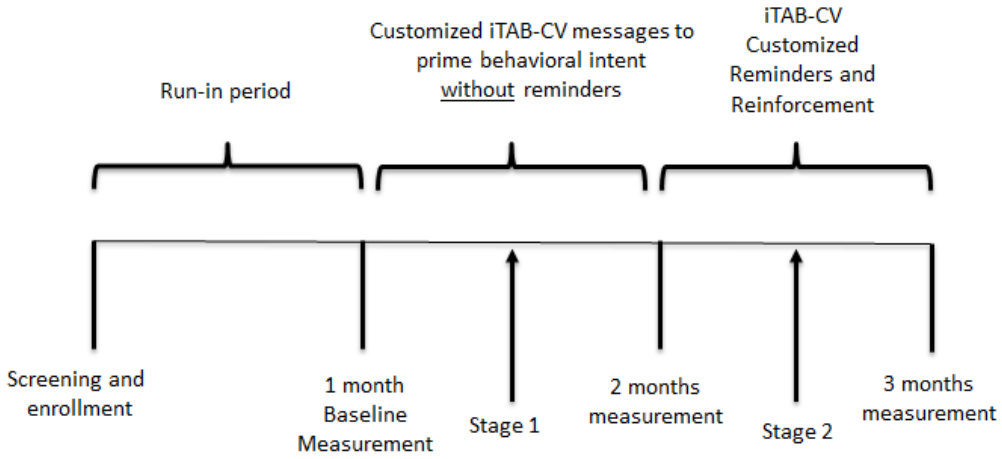

Figure 2: Diagram of Phase II Design

All study participants will be followed for a 3-month period. iTAB-CV, delivered via mobile phone, is intended to be a brief adjunct to standard primary care and mental health treatment. All individuals will continue to receive

treatment as usual with their regular provider(s). Individuals who meet eligibility criteria will have a 30 day run-in period in which their medication adherence will be measured with TRQ and MEMS but without an additional intervention. Following the run-in period, Stage 1 of the iTAB-CV intervention will be introduced. A member of the study team will conduct an interview in order to customize iTAB-CV for each participant at the baseline session. In the first month of iTAB-CV, participants will receive alternating daily texts with psychoeducational and motivational content once daily and a daily mood rating request to both monitor their mood and to determine engagement with the iTAB-CV intervention. In the second stage of iTAB-CV, participants will receive daily texts which will include medication reminders, contextual cues, and immediate reinforcement for medication taking behavior in addition to the content from stage 1. Assessments that include evaluation of treatment adherence, psychiatric symptoms, self-efficacy for medication taking behavior, illness beliefs, medication attitudes, and habit strength for both antihypertensive and BD medications will be conducted at four time points over a 3-month time period (screening, baseline/week 4, week 8, and week 12). Blood pressure will be measured at each of the four contacts. Individuals who drop out of the intervention, and who agree, will be followed up with outcomes assessments over the same 3-month time period that they would have been evaluated had they remained in the study.

Participants:

Inclusion criteria:

1. Participants will have a clinical diagnosis of BD for at least 2 years as determined by a standardized diagnostic interview, the Mini-International Neuropsychiatric Interview (MINI) (52)
2. Have stage 1 or 2 HTN with a systolic pressure ≥130
3. Carry a diagnosis of HTN per patient self-report ≥ 6 months prior to enrollment
4. Have been prescribed at least one regularly scheduled antihypertensive medication for ≥ 3 months since diagnosis
5. Have self-reported poor adherence to at least one antihypertensive medication defined as missing 20% or more of medication within either the past week or past month (53-56) as identified by the Tablets Routine Questionnaire (TRQ)
6. Be able to participate in psychiatric interviews

Exclusion criteria:

1. Unable or unwilling to participate in psychiatric interviews. This will include individuals, who may be too psychotic to participate in interviews/rating scales
2. Unable or unwilling to give written informed consent to study participation
3. Under the age of 21
4. In the interest of patient safety, individuals who are at high immediate risk for suicide will be excluded from study participation. The suicide risk assessment will be informed by standardized assessments of psychiatric symptoms and the Mini-International Neuropsychiatric Interview (MINI). In the event that a potential study participant is determined to be at high risk for suicide, that individual will not be enrolled and the study staff will immediately implement procedures for the safety of the individual. Once such individuals are deemed stable, they may be once again considered for inclusion in the research.
5. Individuals who are monolingual, non-English speaking will be excluded. Given the relatively small sample size in this study, it would not be practical to conduct sub-group analyses. Also, the study assessment tools are not available in other languages and would be impractical to develop. Based upon our BD adherence work, which drew upon a populations similar to this trial, there were no potential subjects who were excluded from the studies due to inability to speak English.
6. Illiterate participants will be excluded because reading is an essential skill required to complete self-report questionnaires administered during the study as well as to utilize the text messaging intervention.
7. Unwillingness to receive text messages

The study will not exclude individuals based on physical health status, although some individuals may choose not to participate because of their own health status. Inclusion criteria for study participation are purposely quite broad in order to represent a “real-world” BD population that typically receives care in clinical settings.

Vulnerable Populations:

Pregnant Women:
According to 45 CFR 46.204, pregnant women may be involved in this research study because the study risks to the pregnant woman and fetus are not greater than minimal risk, and the purpose of the research involves testing a psycho-educational intervention to improve psychiatric treatment adherence which is important for achieving the objectives of the research. Each individual providing consent will be informed of reasonable foreseeable impact of the research on the fetus. There will be no inducement, monetary or otherwise offered to terminate a pregnancy, and individuals engaged in the research study will have no part in determining the viability of a neonate.
If a women becomes pregnant while in the study, she may choose to continue or discontinue participation. Partners of pregnant subjects or pregnant partners of subjects will not participate in this research.

Employees of UHHS and Case:
Employees of UHHS and Case may be included in the study provided the following:

- they are not direct reports to the Department of Psychiatry at UHHS, or the Department of Psychiatry, Department of Neurology, or the Center for Health Care Research and Policy at Case Western Reserve University
- they are not employees of the principal investigator or co-investigators, with direct involvement in the proposed study or other studies under the principal investigator or co-investigators

The informed consent documents contain the standard language informing any potential participant that is an employee that they are not being recruited specifically because of their employee status and that their choice to withdraw from the study does not in any way affect their status as an employee.

Major Psychiatric Illness:
Inclusion of participants with bipolar disorder is necessary, because the main purpose of the study is to find an effective psycho-educational intervention to improve psychiatric treatment adherence in those with bipolar disorder. Those with other major psychiatric illnesses will not be included because this study is specific to only those with bipolar disorder.
Given that the incidence of comorbid psychiatric conditions is high in patients with bipolar disorder, they will not be excluded for having additional psychiatric diagnoses.

Relevant Excluded Populations
Non-English Speaking Participants:
Non-English speaking individuals will be excluded, because study assessment tools are not available in other languages and would be impractical to develop.

Illiterate Participants:
Because reading is an essential skill required to complete self-report questionnaires administered and read text messages during the study, illiterate individuals will be excluded from the study.

Recruitment:
Patients will be recruited by a variety of methods:

- the Principal Investigator's clinical practice
- the Co-Investigators' clinical practices
- Family Practice and Department of Internal Medicine, University Hospitals Cleveland Medical Center
- the inpatient psychiatric unit at the UH Richmond Medical Center: 27100 Chardon RD
  Richmond Heights, OH 44143
- referrals from other mental health providers
- responses from community outreach to different Community Mental Health Centers (CMHC), and other organizations that serve this population
- IRB-approved study flyers

Psychiatrists, primary care physicians, and other clinicians will be asked to discuss this project with eligible individuals. CMHC and other organizations that serve this population will be asked to coordinate introductions of study staff to discuss this project with eligible individuals. Individuals referred with BD 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 in relation to the wider population of people with BD.

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].

Study Personnel:
The study PI 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.

Specific Procedures:
In phase 2, all eligible participants will receive iTAB-CV. After providing informed consent, all participants will undergo screening followed by a 30-day run-in period in which adherence will be measured using eCAP and self-report. During the 30-day run-in period, participants will continue to receive care as usual and serve as their own control with no intervention Participants will be provided with the eCAP device for the antihypertensive agent that is missed most often. In the case of more than one such agent, the antihypertensive dosed most often. If there is again more than one such agent, the most recently prescribed agent will be chosen. Based on our experience with MEMs, the Hawthorne effect wears off after 1-2 weeks. After the 30-day run-in period, participants will receive 30 days of stage one of iTAB-CV. The study PI or study staff will conduct an interview in order to customize iTAB-CV for each participant at the baseline session.

In stage one of iTAB-CV, participants begin receiving 1 daily educational/motivational customized text messages addressing medication attitudes, social influences, and self-efficacy which will alternate between antihypertensives and BD medications without reminders and 1 daily mood rating. Participants will identify any stems that they don't want to receive and can write in their own personalized messages. At the 8 week meeting, the study PI or study staff will conduct a brief 2nd iTAB-CV interview to determine the types of medications taken (antihypertensives and/or bipolar medications) and at which times of day as well as to pick reminders/reinforcement texts that the participant wants to receive for stage two.

Stage two of iTAB-CV includes the addition of customized context cues/reminders and immediate reinforcement for medication taking behavior in addition to 1 daily motivational mood rating. The number of texts per day will be determined based on the number of times a day that medications are prescribed (up to four a day). Assessments that include evaluation of treatment adherence, psychiatric symptoms, health status, self-efficacy for medication taking behavior, illness beliefs, medication attitudes, and habit strength for both antihypertensive and BD medications will be conducted at four time points over a 3-month time period (screening, baseline/week 4, week 8, and week 12). Blood pressure and weight will be measured at each of the four contacts. Height will be measured at screen. Individuals who drop out of the intervention, and who agree, will be followed up with outcomes assessments over the same 3-month time period that they would have been evaluated had they remained in the study. Table 1 outlines the study schedule of events/assessments.

Individuals will receive reminder telephone calls or text messages during the 2 weeks prior to their scheduled appointment. Individuals will be requested to provide three additional contacts who may assist in facilitating contact with the participant should the individual miss follow-up appointments and if difficulty arises in contacting the individual to re-schedule follow-up (for example, change of address or telephone number). In order to optimize study retention, study staff will maintain personal contacts with study participants via greeting/post cards for birthdays and holidays and regular contact for "location checks" between assessment periods.

One month post study completion, the PI or research study staff will call the individual and will administer the TRQ over the phone for bipolar and blood pressure medications.

Intervention:

iTAB-CV Theoretical Basis, Content, Format

Individuals with BD tend to have erratic lifestyles, and the present intervention is not dependent on frequent contact between provider and patient. People with BD have difficulty with adherence and rates of attendance at clinic-based sessions are poor. This intervention circumvents this problem by administering the intervention on a mobile phone.

In iTAB-CV, sending texts is automated. The iTAB-CV intervention is highly scalable within and across patient populations. The majority of effort in a texting intervention is in the initial programming of the automated system. Once the script is in place, the intervention can be extended for longer periods of time, modified to increase the pool of queries and reminders, altered to include additional medications. iTAB-CV is personalized with texts that are specific to the person, medication and timing. Moreover, iTAB-CV uses the participant's own words for both reminders and reinforcers. iTAB-CV asks the participant to respond to reminders and queries so the intervention is interactive unlike an alarm clock or other programmed devices. iTAB-CV is flexible and can send reminders consistent with the participant's schedule. If medications are switched during the study, we can update iTAB-CV. Also, iTAB-CV will randomly select from a possible pool of reminders and reinforcers, assuring that texts do not become stale. The texts will be customized to overcome existing barriers to adherence.

iTAB-CV:

At the initial visit we will gather the following information to personalize electronic reminders about medications according to the following steps:

1) Identify medications: At the initial assessment we will identify the type of medications taken by each participant at what time of day (participants will be asked to bring all medications to their initial appointment) for hypertension and bipolar disorder. For tracking and reminders, we will identify regularly prescribed medicines for hypertension and bipolar disorder.
2) Create categorical description of medications: We will not refer to a specific medication name but rather a medication category (antihypertensive versus bipolar medication) ask participants what name they would like to use to describe this category. We considered using a code name for all participants but those in the 3 patient focus groups indicated that they preferred to use the actual disorder names. Given that it is possible that particular participants may find the name of the disorder stigmatizing, they will have the option to pick their own title to refer to the disorder such as unrelated initials.
3) Create personalized reminders: Participants will create their own personalized reminders and remove stems that they don't like. For example, persons may choose to say: "Remember to take …", or "Your health is important, take…" We will provide a menu of reminder options for participants and they will mark those that they don't want to receive. In order to decrease the tendency to ignore a consistent reminder, the program will be automated to randomly choose and deliver one of the reminder stems created by the participant.
4) Identify ideal time for reminders: We will work with participants to identify the best time to send the reminders in order to comply with prescription recommendations. Reminders will be customized for each medication or group of medications. We will also make note of times that participants don't want to receive texts (before or after a certain time of day).
5) Confirm receipt of message: Participants will be asked to confirm receipt of their message.

A final personalized example of the reminder might be: "Your health is important, remember to take your HTN medication. Please reply 1 to confirm receipt of this message."

We will also send text messages once a week that reinforce good adherence to responding to text messages to keep participants engaged (e.g., "Great job responding to all the messages this week!") (See Appendix #3

for sample texts). If they did not respond, they will be encouraged to do so moving forward (e.g. "We really want to hear from you; we hope you will respond to your messages next week!").

Electronic Reminder Device: We will provide participants with mobile devices and we will purchases bulk 'minutes' in order to provide the text message intervention. Importantly, participants will not be responsible should they lose or break the device. Participants may use the device for other purposes (e.g., phone calls, calendar functions) as they wish. Participants along with research staff will collaboratively identify a time during the day in which the reminders will occur. Once enrolled in the study, participants will receive full compensation even if they miss all reminders.

Psychoeducation and training to use electronic device: All participants will receive a standardized brief psychoeducational presentation with information about hypertension and bipolar disorder as well as training on how to use the electronic device at the 4 week visit.

Participants will respond to a daily mood rating text once a day at the end of the day. Indication of severe low or high moods will trigger an automated text that will direct the participant to go to the ER in case of emergency. After 3 such texts, the system will automatically notify study staff who will follow up with the participant with a phone call.

Measures:
Assessments will be conducted by a Research Assistant trained to administer the study measures.

Diagnosis: Baseline diagnostic assessment of bipolar disorder will be verified with a standardized diagnostic scale, Mini-International Neuropsychiatric Interview 7.0.2 (MINI)(Sheehan et al., 1998).

Adherence:
a. Tablets Routine Questionnaire (TRQ) for antihypertensives and BD medications separately: This self-report measure identifies non-adherence for the past 7 and past 30 days (Scott & Pope, 2002a, 2002b), by measuring the percentage of days with missed doses of a given medication. Adherence will be assessed for each regularly scheduled antihypertensive prescribed for ≥ 3 months. For individuals who are on more than one medication, an average TRQ will be calculated for all antihypertensive medications. Adherence will then be assessed for each evidence-based BD regularly scheduled maintenance medication (lithium, anticonvulsant, antipsychotic) prescribed for ≥ 3 months. For individuals who are on more than one medication, an average TRQ will be calculated for all BD medications. According to our study team's recent work, the correlation between a single "index" drug and all BD drugs was 0.95 providing support for measuring one medication as proxy for medication adherence(M. Sajatovic et al., 2015). PRN medications will not be included for either hypertension or BD.

b. eCAP: Study participants will be given an eCAP device for one of their pill bottles, which will record time/date of bottle opening. eCAP will be used for the antihypertensive medication that the patient missed the most frequently in the past week (in the case of multiple antihypertensive medications missed the same proportion of times, the medication dosed most often will be chosen). This method was chosen over monitoring all medications to limit burden, and is appropriate since eCAP is used to confirm the TRQ. A dose will be counted as "taken" if the bottle is opened within six hours of the prescribed time. We will calculate a percent of doses taken by dividing the number of times the bottle is opened by the number of times it should have been opened as per the prescription. Participants who use organizers rather than bottles will be instructed to open and then shut an empty bottle with an eCAP as a "diary" each time they open their pill organizers. Participants will be given the eCAP at the screening visit if they fit inclusion/exclusion criteria. eCAP will be assessed at the baseline visit based upon pill-taking behavior during the interval between screening and baseline visit. Baseline visits will be targeted at 4 weeks after completion of the screening visit. At screening, participants will be asked when their index drug is up for a refill. They will then be reminded to refill their index drug and fill their eCAP via the iTAB-CV system.

BD Symptoms:

a. **Brief Psychiatric Symptom Scale (BPRS)**: The BPRS is a clinician rated measure that evaluates the spectrum of symptoms seen in individuals with BD (including mania, psychosis, depression and disorganization) (Shafer, 2005).
b. **Montgomery Asberg Depression Rating Scale (MADRS)** (Montgomery & Asberg, 1979): The MADRS measures symptoms of depression. Total scores on MADRS range from 0-60, with higher scores indicating more severe depression.
c. **Young Mania Rating Scale (YMRS)**: The YMRS is a clinician rated measure of mania symptoms. Irritability, speech, thought content, and disruptive/aggressive behavior are doubly weighted and are rated on a 0 to 8 scale. The remaining 7 items are rated on a 0 to 4 scale (Martha Sajatovic et al., 2015).

Additional Measures:

a. **Health resource use in the 3-month period prior to study enrollment and in the 3-month study period (emergency care, hospitalization, outpatient mental health and primary care/other medical care visits)**
b. **Charlson Comorbidity Index (CCI):** Self Report Version - Data on comorbid medical conditions will be collected based on the self-report version of the CCI (Charlson, Pompei, Ales, & MacKenzie, 1987; Chaudhry, Jin, & Meltzer, 2005). The CCI summary score is comprised of the presence of 10 medical conditions including respiratory diseases, rheumatological diseases, cancer, diabetes, digestive problems, heart trouble, HIV or AIDS, kidney disease, liver disease, and stroke. While the original CCI includes dementia, it was excluded from the self-report version given that those with dementia would not be able to provide informed consent. Each disease category is assigned a weight which represents mortality risk with lower scores indicative of lower risk.
c. **Mini-International Neuropsychiatric Interview 7.0.2.(MINI):** The MINI is a diagnostic interview which takes approximately 15 minutes to administer and is based on the DSM and ICD psychiatric disorders (Sheehan et al., 1998).
d. **Medical history**
e. **The Memory for Intentions Screening Test (MIST):** The MIST is a task-oriented measure for prospective memory and takes approximately 30 minutes to administer. This multidimensional task analyzes the skills used to complete the eight tasks that make up the test, and is appropriate for those with neurological disorders (Woods et al., 2008).
f. **Rapid Estimate of Adult Literacy in Medicine –Short Form (REALM-SF):** The REALM-SF is a 7 item measure that identifies patients that are at high risk for having limited health literacy. The measure is quick, taking only a minute or two, and identifies the grade level of the patient if they read below the ninth grade level (Davis et al., 1993).
g. **Brief Illness Perception Questionnaire (Brief IPQ):** The Brief IPQ is a nine item paper and pencil questionnaire that provides a quick assessment of illness perceptions. Each item is rated on a five-point Likert scale (Broadbent, Petrie, Main, & Weinman, 2006).
h. **Medication Adherence Self-Efficacy Scale - Revised (MASES-R):** The MASES-R is a 13 item questionnaire that measures patient's confidence to adhere to their antihypertensive medication regimen under various challenging conditions. The total score ranges from 1-4 and is the average score of all 13 items. Higher scores are indicative of higher self-efficacy (Fernandez, Chaplin, Schoenthaler, & Ogedegbe, 2008).
i. **Self-Report Habit Index (SRHI)**: The SRHI is a 12 item self-report questionnaire that measures habit strength and will be administered regarding the habit of taking medication (Verplanken & Orbell, 2003).
j. **Blood Pressure**: Systolic and diastolic blood pressure will be taken with an automatic blood pressure monitor at each study visit.
k. **Height and Weight/BMI**: Height will be measured at the screen visit and weight will be taken at each visit so BMI can be calculated.

Medication Attitudes Measures:

a. **Beliefs About Medicines Questionnaire (BMQ):** The BMQ is an 18-item measure split into two sections, one for beliefs regarding medication in general and one for beliefs about an individual's own prescribed medications (Horne, Weinman, & Hankins, 1999; Ruppar, Dobbels, & De Geest, 2012).
b. **Attitude toward Mood Stabilizers Questionnaire (AMSQ):** A modification of the Lithium Attitudes Questionnaire, the 19-item AMSQ evaluates an individual's attitudes towards psychiatric medication (Chang, Sajatovic, & Tatsuoka, 2015).

Clinician involvement:
Individual iTAB-CV interviews will be administered by the study PI or by a trained research team member. Clinician buy-in remains important. Providers will be encouraged to refer patients they believe are sub-optimally adherent.

Providers will be notified of participant enrollment in the study.

Risks associated with study participation:
This study involves completing a set of self-report instruments, along with rating interviews and an intervention customization interview. All of these instruments have been utilized in outpatient research settings and are not associated with risks to patients. The iTAB-CV intervention to enhance treatment adherence involves the use of cognitive and behavioral strategies including psychoeducation, motivational interviewing, context cues/reminders, and positive reinforcement all delivered via text messaging.

The risks to the subjects will be primarily those of talking about some matters, which they may find uncomfortable. Participants do not have to answer upsetting questions, and may discontinue the interview if they wish. It is also possible that the intervention will have no effect on treatment adherence and that receiving texts may become an annoyance. Participants have the option of not responding to texts. They can also stipulate times of the day during which they don't want to receive texts.

Furthermore, the text messages will query regarding daily mood ratings. These approaches are not generally known to increase risk to individuals. Individuals with bipolar disorder are already at risk for depression and possible suicidality. While this intervention is unlikely to increase these risks, it may be able to detect them more readily given the daily mood ratings. There is an automated texting sequence to address texts indicating severely low or high mood which will provide the participant with information on how to access immediate emergency services. If there are 3 such mood ratings in a row, an automatic text will be sent to the research assistant who will follow up by phone with the participant.

The study requires that participants receive medication reminders to take medications as well as answer daily questions about their mood on their mobile device. If a participant chooses to store personal information on this device, it is possible that if the device were lost, the confidentiality of the participant may be compromised. It is possible that participants could put personal information on the device that could link to the delivered text messages, but the risk of losing confidential information in this way is exactly the same as the risk incurred by owning and using any cellular phone. The text messages used in this study are not specific to bipolar disorder and are purposefully generic. Reminders do not use medication names but rather category of medication (high blood pressure medicine or bipolar medicine) and the mood question is generic. While participants in the patient focus groups indicated that they prefer to have the text messages use the actual name or their disorder, participants will have the option of choosing an alternative name if they wish. The text messages will be delivered from a generic phone number that will not be linked to the specific study goals.

If the phone were to be lost, persons could find responses to medication and mood queries. This will be clearly articulated to participants as a study risk and is specified in the consent document. If participants are uncomfortable with this risk, they may choose not to enroll in the study.

Participants will have their blood pressure taken 4 times over a 12-week period. There is minimal risk to blood pressure readings.

The study requires the participant to place a device on top of a standard pill bottle which may compromise the use of pill organizers or other devices to manage their medications. This may affect their medication adherence.

Participants may choose not participate in the study and this will not in any way affect their regular care with clinicians. Individuals who do choose to participate in the study will continue to receive treatment as usual from their regular care provider(s).

It is possible that the subjects' physical or mental health may worsen during their participation. Subjects will be in close communication with the research study team to make sure they are monitored for unexpected worsening and that the appropriate measures are taken.

Subjects will be free to withdraw from the study at any time without penalty. If during the course of the assessment, the subject communicates to the rater or investigator that the subject may be in immediate danger or at acute risk of harm to self or others, (for example, reporting a suicide plan), the study staff interacting with the individual will immediately notify 1) The patient's clinician and 2) The study PI so that all available and appropriate measures may be taken to ensure the prompt safety and most appropriate care setting for the patient. If at any point a subject presents with what are deemed to be unsafe blood pressure readings (i.e. ≥170mg Hg), the study PI, psychiatrist-investigator or internist-investigator will be notified. The study staff will notify the subject's clinician and accompany them to the ER if it is deemed necessary.

Potential benefits associated with study participation:
It is the goal of this project to contribute knowledge regarding adherence attitudes and effective interventions to improve treatment adherence. It will be explained to subjects that their participation in the study may not benefit them directly. Participants may benefit from participation (e.g. improved symptoms). The iTAB-CV intervention is hypothesized to improve adherence, lower systolic blood pressure and decrease psychiatric symptoms.

Alternatives to Study Participation
While participating in this study subjects will continue to receive their usual treatment, including medication prescriptions from their regular mental healthcare provider. Therefore, the alternative to participating in this study is to not participate.

Compensation for research participation:
To help cover their costs and reimburse them for their time and effort, each subject will be compensated $40 for the screening visit and $30 for each of the remaining three assessments: baseline (4 weeks), visit 1 (8 weeks), and visit 2 (12 weeks). Additionally, participants will receive $10 for bringing the eCAP to each of the baseline, 8 week, and 12 week visits. Participants will be given bus or parking passes with approximately a $5 value for transportation for each assessment if needed. Each participant for phase 2 will potentially receive a total of $160 plus $20 for transportation if needed. Participants will either be paid by a check mailed to them or petty cash. Transportation reimbursement will be given in the form of a bus pass, a parking voucher, or in rare cases, cash at the time of the visit. Participants will also be able to keep the cell phones provided to them at baseline and unlimited texting from baseline until their completion in the study.

Cost to participants:
Participants and their insurance will not be charged for any study visits, phones and free texting are provided for the duration of the study. Subjects may incur costs such as travel, parking, and meals. These are reasonable costs that a subject will incur as a result of going to study visits. Subjects are compensated for these costs as outlined above.

Compensation for research-related injury:
If injury occurs as a result of a subject's involvement in this research, medical treatment is available from University Hospitals or another medical facility but the subject or their medical insurance will be responsible for the cost of this treatment. There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury.

Plan for Obtaining Informed Consent:
There will be three layers built into the consent process.
First, all providers and research personnel will be prescreening patients for capacity to give consent – assessing both static factors (e.g. comorbid diagnoses such as intellectual disability) and dynamic factors (e.g. acute psychopathology). Those who are deemed permanently unable to give informed consent will be excluded from studies. Clinicians will be instructed to defer referral of those with severe acute symptomatology until the patient is able to consent, i.e., severe mania accompanied by psychotic thinking.
The second layer is an informal evaluation by study staff of the individual's capacity to give consent to participate. Individuals who are deemed capable of giving informed consent then proceed with screening and enrollment. An authorized member of the investigational staff will explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care they will receive for the treatment of their disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice any possible future treatment. The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions.
Potential participants are provided with the written copy of the consent form with HIPAA language, which they are asked to read and review fully. Following this, the researcher asks whether the participant has any questions and then orally summarizes all the points covered in the informed consent, again inquiring if there are any questions. Prospective participants will be asked to explain what the study will involve in their own words to confirm their understanding. At this point, the third layer is employed by asking subjects questions relevant to the content of the consent form to make sure they have retained vital information and know what they are consenting to participate in (see attached consent quiz). If the subject agrees to participate, the researcher and subject sign the consent form prior to participation. A copy of the signed and witnessed consent form will be given to each subject. The research assistant will then record in the medical record that the consent was obtained and that the decision to participate in the research was "informed".

Due to the nature of bipolar disorder, a patient may be considered "impaired" in decision making capacity due to mania or depression, not due to cognitive impairment. These individuals may be deemed "legally incompetent" and may have a court appointed legal guardian under the statutes of the State of Ohio. If a patient with a legal guardian meets the study's inclusion criteria, the investigator will discuss the study with both the patient and the legal guardian. After obtaining proof of guardianship, both parties will be asked to consent to the patient's participation. If either the patient or the guardian declines to participate, the patient will not be enrolled in this study.

The person obtaining consent will complete the Consent Process document and will file it with the signed consent form in a secure file cabinet separate from the participant's study documents

Participant privacy:
Privacy language is included in the informed consent form. Participants must be willing to allow the sharing of information between the research team and their regular mental health and primary care providers. Participants have the option of withdrawing from the study at any time and can request that no further information be shared about them from that point on. Data that were collected prior to their withdrawal will be de-identified and will still be used in the data analysis for the study.

Data confidentiality
The study personnel at UHCMC whose responsibilities require access to personal data agree to keep the identity of study subjects confidential. Study data will be collected and managed using REDcap (Harris et al., 2009), a secure, web-based application designed to support data capture for research studies.

Careful attention will be given to confidentiality, which will be maintained using subject identification (ID) codes. Study ID codes will be the basis for linking information from data and results. Audio recordings will be assigned their respective subject code. Research files are not available to any unauthorized person. The list that links

study ID codes with subject names and all forms bearing subject names will be stored in a password protected file in a folder only accessible to research team personnel on the secure UH server.

A Certificate of Confidentiality has been secured from NIMH by the investigators.

Data security:
Research files are not available to any unauthorized person. Research data are collected and stored using UH REDCap. Any paper assessment forms are stored in file cabinets in the locked research offices of the PI on the 7th floor of the W.O. Walker Center at 10524 Euclid Ave. Cleveland, Ohio. The list that links study ID codes with subject names and all forms bearing subject names will be stored in a password protected file in a folder only accessible to research team personnel on the secure UH server and/or REDCap. Data analysis files will also be stored in the secure folder on the UH network.

Data Safety and Monitoring will be the responsibility of 1) The study's principal investigator (Dr. Levin), 2) The local Institutional Review Board (IRB), and 3) a DSMB.

With regard to loss of confidentiality associated with the mobile device, no personally identifying information will be texted by the study team or stored on the device unless the participant chooses to do so. Therefore, if a device is misplaced, there is minimal likelihood that any loss of confidential information will occur.

Adverse events will be assessed and recorded at every visit following the Screening visit. Assessments will include observations by investigators, spontaneous reporting by subjects, and standard non-leading questions. For every adverse event, the PI will provide an assessment of the severity, duration and causal relationship to study intervention, and document all actions taken with regard to study intervention, as well as any other treatment measures for the adverse event. If an outcome for an adverse event is not available at the time of initial report, follow-up will proceed until the outcome is known.

For the purposes of this investigation, a serious adverse event will be defined as any untoward medical occurrence believed to be possibly or probably due to the study and:

1. Results in death
2. Is life threatening
3. Results in persistent or significant disability
4. Is a congenital anomaly
5. Is an important medical event that may not be immediately life threatening or results in death or hospitalization

If serious and unexpected adverse events occur, or any other unanticipated problems involving risks to subjects or others, the IRB will be notified. This notification will indicate what serious adverse events were noted, whether they appeared related to the trial, and whether the trial was approved to continue. If found to be related to the trial, the PI will institute appropriate procedures, notify the NHLBI Project Officer, and report such events to appropriate institutional officials and the Office for Human Research Protections.

Data Analysis plan: The aim of this project is to test the use of iTAB-CV in a pilot feasibility, acceptability and preliminary efficacy study in a sample of 38 individuals with BD and HTN. Hypothesis: iTAB-CV will be feasible to conduct in an outpatient setting, will be acceptable to participants, and will be associated with improved HTN medication adherence among at-risk individuals with BD and HTN. Treatment acceptability/satisfaction will be measured via a self-report questionnaire and feasibility will be evaluated by percentage of texts answered. The primary dependent measure will be treatment adherence of antihypertensives evaluated with Tablets Routine Questionnaire (TRQ). Adherence will also be measured objectively through eCAP. The measurements will be taken at screening, baseline (4 weeks), 8 weeks, and 12 weeks follow-up. Of primary inferential focus is whether there is change in adherence from baseline to 12 weeks. Adherence will be calculated as a proportion of prescribed medications taken in the past week and will be assessed for each regularly scheduled maintenance agent for HTN prescribed for three months or longer on a daily, routine basis. For individuals who are on more than one such agent, adherence will be assessed for each agent and an average will be

calculated. TRQ will be the main adherence measure, but eCAP will also be analyzed and compared with the TRQ. Secondary outcome measures are: Systolic blood pressure, TRQ for antipsychotic and/or mood stabilizers, psychiatric symptoms (BPRS health utilization, Medication Adherence Self-Efficacy Scale - Revised, Self-Report Habit Index (64), Brief Illness Perception Questionnaire, Beliefs About Medicines Questionnaire, AMSQ, treatment acceptability/satisfaction by questionnaire and exit interviews, and feasibility via % texts answered.

Main Hypothesis Testing: A paired t-test will be used to test significance for the TRQ and eCAP adherence outcomes from baseline to 12-week follow-up. Nonparametric tests will also be considered. Secondary Hypothesis Testing: Difference from baseline to 8 weeks, and 8 weeks to 12 weeks will also be analyzed. Corresponding TRQ and eCAP values will be correlated and Bland-Altman plots will be used to help identify discrepancies. Correlations will be computed for change in antihypertensive adherence values versus changes in TRQ for antipsychotic and/or mood stabilizers, medication attitudes, self-efficacy, and habit strength. Exploratory longitudinal mixed models will be used to analyze repeated measurements at baseline, 8 weeks, and 12 weeks. Note that the preliminary analyses and model estimates will inform the future design of a more extensive study involving a controlled trial.

Attrition Analyses: Preliminary analyses will determine factors that are associated with attrition effects. Attrition rates in a current BD adherence study at our institution is < 30%. Differential attrition by key covariates such as age and gender will be examined, such as through log rank tests. Power Analysis: Given the preliminary data from a prior BD adherence study (35), difference in oral medication adherence after treatment was 21.7%. Standard deviation of this difference was 39%, resulting in an effect size of 0.56. We expect to observe a similar if not greater effect size. Using a t-test of difference between baseline and 12 week TRQ, power is 0.80 at two-sided alpha = 0.05 for a sample of 38 subjects to reject a null hypothesis of no change in adherence when effect size is 0.549, and attrition is 25%. The projected sample size should thus provide adequate power to detect expected changes in anti-hypertensive drug adherence levels.

Table 1: Schedule of Assessments and Study Events

Procedure	**Screen**	**Baseline**	**Visit 1**	**Visit 2**
Visit Timing	**Day 0**	**Week 4**	**Week 8**	**Week 12**
Informed Consent	X			
Inclusion/Exclusion	X			
Demographics, Charlson, medical history	X			
Diagnosis: Mini-International Neuropsychiatric Interview	X			
Prospective Memory: The Memory for Intentions Screening Test (MIST)	X			
Rapid Estimate of Adult Literacy in Medicine – Short Form (REALM-SF)	X			
Brief Illness Perception Questionnaire (Brief IPQ)	X		X	X
Medication Adherence Self-Efficacy Scale - Revised (MASES-R)	X		X	X
Medication Attitudes – Beliefs About Medicines Questionnaire, AMSQ	X		X	X
Self-Report Habit Index	X	X	X	X
Primary outcomes: Average TRQ for antihypertensive agents eCAP for antihypertensive agent	X	X X	X X	X X
Secondary outcomes: Systolic Blood Pressure Height (Screen only) and weight / BMI Average TRQ for bipolar medications	X X X	X X X	X X X	X X X
Brief Psychiatric Rating Scale (BPRS)	X	X	X	X
Montgomery-Åsberg Depression Rating Scale (MADRS)	X	X	X	X
Young Mania Rating Scale (YMRS)	X	X	X	X
Introduction of eCAP for antihypertensive	X			
Brief powerpoint presentation providing psychoeducation on hypertension and bipolar disorder		X		
iTAB-CV interview and training; iTAB-CV stage 1 - initiation of behavioral priming via text + daily mood monitoring; phone given at this time		X		
iTAB-CV stage 2 – brief interview regarding iTAB-CV; frequency of text; choose stems for reminders and reinforcement			X	
Participant acceptability/satisfaction/feasibility/exit interviews				X

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