Mood Stabilizer Plus Antidepressant versus Mood Stabilizer Plus Placebo in the Maintenance Treatment of Bipolar Disorder

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SUMMARY OF PROTOCOL

Patients with bipolar I disorder (BD) experience depression 3 times more frequently than mania, and antidepressants are prescribed as adjuncts to mood stabilizers in up to 70% of patients. However, no placebo-controlled trials have assessed the efficacy or safety of modern antidepressants in combination with mood stabilizers in the maintenance treatment of BD. We propose a multicentre, randomized, double-blind clinical trial comparing mood stabilizer plus antidepressant (escitalopram or bupropion XL) to mood stabilizer plus placebo in the maintenance treatment of BD. The trial will consist of two phases:

Open-Label Acute Treatment Phase
Patients with BD depression who are receiving treatment with antimanic medication(s), defined as: 1) a mood stabilizer (lithium or divalproex), 2) a second-generation antipsychotic (SGA) (risperidone, olanzapine, quetiapine, aripiprazole, or ziprasidone), or 3) combination anti-manic therapy (two mood stabilizers; or a mood stabilizer plus an SGA (the SGA asenapine will also be permitted if prescribed with a mood stabilizer); or a mood stabilizer or SGA plus lamotrigine), will have open-label escitalopram 10-30 mg/day or bupropion XL 150-450 mg/day added to their medication(s) for up to 16 weeks. (Because of their potent antidepressant properties, patients who are taking lamotrigine or quetiapine in conjunction with a mood stabilizer, or who are taking quetiapine alone, must have non-response to these medications established over a 6 week trial before antidepressants are commenced.) The primary outcome for the open-label phase is mean improvement in Montgomery-Asberg Depression Rating Scale (MADRS) scores from baseline to endpoint. We will also measure rates of response, remission, and treatment-emergent mania and hypomania; overall psychiatric status and improvement; rates of adverse events (AEs) and serious adverse events (SAEs); and quality of life. Patients who receive at least 4 weeks of treatment and achieve remission from their index depression for ≥ 2 weeks will be eligible to enter the double-blind maintenance study phase. Enrolment in the double-blind phase must occur within 8 weeks of remission. The duration of the open-label phase will be 4-16 weeks, depending on time to remission.

Double-Blind Maintenance Treatment Phase
Patients may enter the double-blind phase either 1) following completion of the open-label phase, or 2) within 2-8 weeks of remission from a documented depressive episode that was treated with the same medications used in the open-label phase. (Patients who are taking carbamazepine plus an antidepressant cannot enter the open-label phase, as carbamazepine can unpredictably reduce antidepressant serum levels, and this could affect the results of the open-label phase, but patients who respond to clinical treatment with carbamazepine plus an antidepressant will be assumed to have adequate antidepressant serum levels, and may thus be enrolled in the double-blind phase.) All patients entering the double-blind phase will continue treatment with their anti-manic medication(s) and will be randomized to one of two treatment arms for up to 52 weeks:

- Patients randomized to the "**8 week arm**" will discontinue antidepressant treatment after 8 weeks, as recommended in current clinical practice guidelines. The antidepressant will be tapered in a double-blind manner beginning at 6 weeks, and will be substituted with placebo by 8 weeks.

- Patients randomized to the "**52 week arm**" will continue treatment with their antidepressant medication for 52 weeks, or until withdrawal from the study.

The primary outcome measure for the double-blind phase is mean survival time in the study until the occurrence of any mood episode (manic, hypomanic, or depressive), as determined using Kaplan-Meier survival analysis. We will also measure mean time to manic or hypomanic episode; time to depressive episode; time to study discontinuation for any reason (eg. onset of mood episode, intolerable side effects, patient or clinician decision); the proportion of patients who experience any mood episode, a manic or hypomanic episode, or a depressive episode; the percentage of patients who experience subsyndromal symptoms and percentage of time spent with subsyndromal symptoms; rates of AEs and SAEs; and quality of life.

BLOOD SAMPLES

Pharmacogenetics and Epigenetics (Optional for Sites)

The prediction of medication response and side effects based on individual genetic variation and the epigenetic regulation of gene expression is a rapidly growing area. However, few studies have examined the association between antidepressant response and single nucleotide polymorphisms, or between response and gene regulation via CpG methylation, histone acetylation, and other epigenetic mechanisms. The design of this study offers a unique opportunity to examine genetic and epigenetic predictors of drug response and side effects, such as antidepressant-induced mania. Examination of genetic and epigenetic markers associated with norepinephrine, serotonin, dopamine, GABA, glutamate, N-acetyl-aspartate and second messenger systems will be conducted. Cell lines will be established to allow for adequate testing timelines. Blood samples for genetic and epigenetic testing will be collected at four time points: 1) at enrolment into the study, 2) two weeks after the criteria for treatment response are met, 3) 12 weeks after randomization in the double-blind treatment phase, and 4) at study endpoint. All blood samples collected will be stored and analyzed at UBC.

Measurement of Serum and Intracellular Neurochemicals (Optional for Sites)

A variety of neurochemical markers have been implicated in the pathophysiology of bipolar disorder and its response to treatment. Many of these substances are easily measured in serum or in the cytoplasm of blood cells, and may reflect levels in the central nervous system. Examples of serum markers include the neurotrophins such as brain derived neurotrophic factor (BDNF), which are potential candidates in the pathophysiology of bipolar disorder, and in particular the cognitive impairment that is associated with it. Other neurotrophins like glial derived neurotrophic factor (GDNF) have been found to be altered during mood episodes. Data from preclinical studies also showed changes in nerve growth factor (NGF) in an animal model of mania. Intracellular biochemical cascades such as the oxidative stress cascade and second messenger systems will also be investigated, as substantial evidence from our group and others implicates them in the pathophysiology of bipolar disorder. Blood samples for the measurement of serum and intracellular neurochemicals will be collected at the same time points as above. All blood samples collected will be stored and analyzed at UBC.

NEUROCOGNITIVE ASSESSMENT(Optional for Sites)

Emerging neuropsychological studies on cognition in euthymic bipolar patients confirm that there are deficits in multiple domains that persist even after the mood symptoms remit. The majority of these studies do not account for the possible effects of treatment, in part due to the lack of homogenicity between samples. By utilizing a neurocognitive battery during the double-blind phase at baseline, week 10, and week 24 we will be able to compare the effects of bupropion and escitalopram to placebo in domains of processing speed, attention/vigilance, as well as verbal and working memory using tests that have been utilized in studies of bipolar and unipolar depression.

The battery will consist of the NAART (at baseline only to control for the effects of IQ on other measures), Verbal Fluency (animal naming), HVLT, Trail Making Tests parts A and B, WAIS-IV Letter/Number Subtest, WAIS-IV Digit/Symbol Subtest, and the Stroop Task.

FINGERNAIL SAMPLING (Optional for Sites)

Measurement of Cortisol:DHEA ratio

The hypothalamic-pituitary-adrenal (HPA) axis, which has consistently been found dysfunctional in patients suffering from a mood disorder, mediates the body's response to stress through secretion of neurosteroids such as cortisol and dehydroepiandosterone (DHEA). These hormones have receptors in limbic regions including the prefrontal cortex and hippocampus; supporting findings that suggests HPA hyperactivity and raised cortisol secretion may cause or exacerbate cognitive impairment and depressive symptomology, although difficulties in interpreting this data arise due to limitations in current sampling techniques which only provide information on hormonal levels over a short time period. By using fingernail analysis of the cortisol:DHEA ratio, we will be able to assess long term HPA activity (as DHEA is thought to play a role in protecting the brain from the negative effects of cortisol, the cortisol:DHEA ratio is considered to be the more accurate measurement of functional hypercortisolemia).

We will take fingernail clippings from subjects at the double blind phase weeks 12, 24, and 36 which are reflective of chronic HPA activity levels surrounding cognitive testing sessions at weeks 0, 10, and 24 respectively, corresponding with different stages of antidepressant treatment or withdrawal. Participants will be asked to trim their nails 2 weeks prior to collection so that samples acquired represent 2 weeks of growth. As phase of menstrual cycle has been known to affect HPA activity, this information will also be collected for premenopausal female participants. All fingernail samples collected will be stored and analyzed at UBC.

INTRODUCTION

Although bipolar I disorder (BD) is defined by the occurrence of manic episodes, patients experience depression 3 times more frequently than mania [1]. While the consequences of mania are well known – occupational disability; relationship difficulties; the consequences of spending, drug use, impulsive sexual activity - depressive symptoms have at least as severe an impact on health and functioning [2]. The mood stabilizing medications lithium and divalproex and the second-generation antipsychotics (SGAs) risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone have all been demonstrated to prevent mood

episodes during the long-term treatment of BD. However, commonly-used maintenance treatments are more effective in preventing mania than depression [3-5]. Not surprisingly, then, **antidepressants are prescribed for up to 70% of patients with BD [6-8], and half of patients prescribed antidepressants continue to take them for one year or longer [9].**

However, to date no double-blind placebo-controlled RCTs have directly assessed the efficacy and safety of modern antidepressants such as escitalopram or bupropion when given as adjuncts to mood stabilizing medications or SGAs in the maintenance treatment of BD. Given the lack of evidence from well-designed placebo-controlled trials, Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical practice guidelines recommend that antidepressants be discontinued 2-4 months after the remission of an acute depression [10]. However, if escitalopram and bupropion are effective in preventing depression without increasing the risk of mania, then clinicians who follow clinical practice guidelines are putting their patients in jeopardy of increased depressive relapses. If, on the other hand, escitalopram and bupropion are ineffective in preventing depressive episodes, or if they lead to an increased frequency of manic episodes that outweighs their antidepressant effect, then large numbers of patients are being prescribed unnecessary and potentially dangerous medications. **The paucity of truly effective treatments for the prevention of BD depression, the frequency of prescription of antidepressants, and the lack of data regarding their effectiveness provide a compelling rationale for a well-designed double-blind placebo-controlled trial to assess their long-term efficacy and safety.**

OBJECTIVES AND STUDY DESIGN

Our **primary objective** is to answer a highly relevant clinical question:

> In clinically representative patients with BD depression who respond to acute treatment with escitalopram or bupropion XL in combination with anti-manic medication(s), does continuing antidepressant treatment for 12 months reduce the risk of relapse into any mood episode, including depression, mania, and hypomania, compared to discontinuing the antidepressant and substituting it with placebo after 2 months?

Our **secondary objectives** are to answer the following questions:

1. Does continuing antidepressant treatment for 12 months reduce the risk of relapse into depression?
2. Does continuing antidepressant treatment for 12 months increase the risk of developing a manic or hypomanic episode?
3. Do rates of subsyndromal mood symptoms and adverse events differ between patients who continue antidepressant treatment for 12 months compared to those who stop the antidepressant after 2 months?
4. Does 12-month antidepressant treatment improve overall health and quality of life for patients, compared to stopping treatment after 2 months?

Study Design
We propose a multicentre, randomized, double-blind, placebo-controlled trial in patients with BD who are currently experiencing a depressive episode. The trial will consist of two phases: an open-label acute treatment phase, and a double-blind maintenance treatment phase. Participants will be recruited from 7 Canadian Centres and 4 Korean Centres.

OPEN-LABEL ACUTE TREATMENT PHASE

Experimental Design
Patients with BD depression (defined as a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥ 20) who are receiving treatment with either a mood stabilizer (lithium or divalproex), an SGA (risperidone, olanzapine, quetiapine, aripiprazole, or ziprasidone), or combination treatment with two mood stabilizers, or a mood stabilizer plus an SGA (asenapine will also be permitted if prescribed with a mood stabilizer), or a mood stabilizer or SGA plus lamotrigine), will have open-label escitalopram 10-30 mg/day or bupropion XL 100-450 mg/day added to their anti-manic medication(s) for up to 16 weeks.

- The choice of the antidepressant (escitalopram or bupropion XL) will be made clinically by the study psychiatrist in collaboration with the patient.
- Patients may add the antidepressant to ongoing anti-manic treatment, or may commence treatment with anti-manic medication(s) and an antidepressant concurrently. Patients who are taking lamotrigine or quetiapine in conjunction with a mood stabilizer, or patients who are taking quetiapine alone, must have non-response to these medications established over a 6 week trial before antidepressants are commenced, as these medications themselves have well-established antidepressant properties.
- The dose of the antidepressant will be titrated by the study psychiatrist as needed and as tolerated until the patient achieves remission from the index depression.
- Dosage changes in the anti-manic medication(s) will also be permitted, as needed and as tolerated, at the discretion of the study psychiatrist.

Patients will be assessed every 2 weeks, or more frequently if clinically indicated, during the open-label phase.

Patients who complete at least 4 weeks of treatment and achieve remission from their index depression which is maintained for ≥ 2 weeks will be eligible to enter the double-blind study phase. Enrolment in the double-blind phase must occur within 8 weeks of remission. The duration of treatment in the open-label phase will be 4-16 weeks, depending on the time required to achieve remission.

Inclusion Criteria
Patients meeting **all** of the following criteria will be eligible for **inclusion** in the open-label study phase:

1. Diagnosed with BD, current episode depressed, with a MADRS score ≥ 20 at both the screening and baseline assessments.
2. The duration of the current depressive episode is ≥ 2 weeks but ≤ 52 weeks.

3. Taking or initiating treatment with an anti-manic medication at a therapeutic dose. If commencing treatment with lithium or divalproex at the screen visit, serum levels must be within the therapeutic range prior to randomization in the double blind phase.
4. Anti-manic medications and therapeutic doses are: lithium, serum level 0.6-1.4 mEq/L; divalproex, serum level 350-700 mM; risperidone 1-6 mg/day; olanzapine 5-30 mg/day; quetiapine IR or XR 300-900 mg/day; aripiprazole 10-30 mg/day; and ziprasidone 80-160 mg/day. Combinations of these medications as outlined above, or the combination of any of them with lamotrigine 100-400 mg daily, or the combination of a mood stabilizer plus asenapine 5-20 mg/day, are also permitted. If taking any other psychoactive medication (other than lorazepam ≤ 4 mg/day or equivalent), is agreeable to tapering and discontinuing it over a period of ≤ 4 weeks.
5. If female and of childbearing potential, is using an adequate method of contraception. Adequate methods of contraception include abstinence; oral contraceptive pill or surgically implanted device; intra-uterine device; condom plus spermicidal foam or jelly; or tubal ligation.
6. Aged 18-70 years, inclusive.
7. Fluent in English and capable of providing informed consent.

Exclusion Criteria

Patients meeting **any** of the following criteria will be **excluded** from the open-label study phase:

1. Has a history of rapid cycling, defined as ≥ 4 mood episodes in the preceding 12 months.
2. Has current manic, hypomanic, or subsyndromal hypomanic symptoms, defined as a Young Mania Rating Scale (YMRS) score ≥ 8 at the screening or baseline visits.
3. Has previously been refractory to treatment with both escitalopram *and* bupropion XL, or has been unable to tolerate both medications due to intolerable side effects or an allergic reaction.
4. Is taking monoamine oxidase inhibitors, such as phenelzine or tranylcypromine.
5. Escitalopram is contraindicated in patients taking the antipsychotic medications pimozide or ziprasidone. Patients on pimozide or ziprasidone can participate in the study and will be prescribed bupropion XL.
6. Bupropion XL is contraindicated in patients taking other preparations containing bupropion, such as Zyban and Wellbutrin SR; in patients with active eating disorders, including anorexia nervosa and bulimia nervosa; and in patients with seizure disorders. Patients with any of these can still participate in the study and will be prescribed Escitalopram.
7. Has active substance dependence, other than caffeine or nicotine dependence, in the preceding 3 months. Otherwise, patients with comorbid substance abuse or other comorbid psychiatric illnesses will be eligible to participate in the study.
8. Is at high risk for suicide, as defined by a score of ≥ 4 on the suicide item of the MADRS, or in the opinion of the investigator.

9. Has an unstable medical illness, as defined by a change in medication or other treatment in the past 4 weeks, or in the opinion of the investigator.
10. Has significant abnormalities on an electrocardiogram.
11. Is pregnant or lactating.

Medications and Dosages

Study Medications
Escitalopram will be provided in 10 mg tablets. Bupropion XL will be provided in 150 mg tablets. Placebo tablets identical in appearance to the study medications will also be provided.

Mood Stabilizers and SGAs
All of the mood stabilizers and SGAs we have chosen for this study are routinely prescribed in the clinical management of BD. Patients will be responsible for covering the cost of these medications.

Open label phase treatment
All patients will be treated with **one antidepressant** (escitalopram or bupropion XL) in combination with **either:**

1. **one or two mood stabilizers** (lithium or divalproex), or
2. **one SGA** (risperidone, olanzapine, quetiapine, aripiprazole, or ziprasidone), or
3. **one mood stabilizer plus one SGA (including asenapine)**, or
4. **one mood stabilizer or one SGA plus lamotrigine**

Antidepressants
Escitalopram will be initiated at a dose of 10 mg daily.

- The dose may be increased in increments of 10 mg at the discretion of the study psychiatrist, until remission of the index depression.
- In patients who develop intolerable side effects, the dose may be decreased in 10 mg increments.
- The total dose must remain within the range of 10-30 mg daily. Patients who are unable to tolerate a minimum dose of 10 mg daily will be discontinued from the study.

Bupropion XL will be initiated at a dose of 150-300 mg daily

- The dose may be increased in increments of 150 mg, at the discretion of the study psychiatrist, until remission of the index depression.
- In patients who develop intolerable side effects, the dose may be decreased in 150 mg increments.
- The total dose must remain within the range of 150-450 mg daily. Patients who are unable to tolerate a minimum dose of 150 mg daily will be discontinued from the study.

Mood Stabilizers and SGAs
Mood stabilizers and SGAs will be prescribed in the following doses:

- Lithium will be prescribed at a dose sufficient to produce a serum level of 0.6-1.4 mEq/L. This usually requires 900-1800 mg/day
- Divalproex will be prescribed at a dose sufficient to produce a serum level of 350-700 mM. This usually requires a dose of 750-1750 mg/day
- Risperidone 1-6 mg/day
- Olanzapine 5-30 mg/day
- Quetiapine IR or XR 300-900 mg/day
- Aripiprazole 10-30 mg/day
- Ziprasidone 80-160 mg/day
- Asenapine 5-20 mg/day
- Lamotrigine 100-400 mg/day

Mood stabilizer dosages may be increased in the usual increments at the discretion of the study psychiatrist:

- lithium 150-600 mg
- divalproex 250-500 mg
- risperidone 1-2 mg
- olanzapine 5-10 mg
- quetiapine IR or XR 50-100 mg
- aripiprazole 5-10 mg
- ziprasidone 40-80 mg
- asenapine 5-10 mg
- lamotrigine 25-50 mg

In patients who develop intolerable side effects, the doses may be decreased in the same increments. The total dose must remain within the specified ranges. Patients who are unable to tolerate the minimum doses will be discontinued from the study.

A blood sample will be drawn to measure serum levels of lithium or divalproex in patients taking these medications at the screening visit, 8 weeks, at endpoint of the open-label phase, and as clinically indicated.

Concomitant Psychiatric Treatments
Concomitant psychiatric medications permitted to control anxiety or insomnia during the open-label study phase include:

- Lorazepam (maximum dose 4 mg daily)
- Clonazepam (maximum dose 2 mg daily)
- Temazepam (maximum dose 30 mg daily)
- Zopiclone (maximum dose 15 mg daily).

No other psychoactive medications are permitted.

Other psychiatric treatments, including ECT, light therapy, and psychotherapy are not permitted. All patients will receive psychoeducation and counselling regarding sleep

hygiene, healthy daily routines, substance abuse, anxiety management, conflict resolution, and problem solving as clinically indicated.

Concomitant Non-Psychiatric Treatments
Medications used to treat underlying stable organic illnesses (*eg.* antihypertensives, thyroid supplements) are permitted, provided the dose of the medication has been stable for at least 4 weeks prior to trial entry, and the dose is expected to remain stable throughout the trial.

Use of herbal medicines such as St. John's Wort is not permitted during the study.

All concomitant medications must be documented on the Case Report Form (CRF). For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition must be documented on the Adverse Event Form of the CRF.

Study Visits and Measures
Procedures for study visits during the open-label phase are summarized in Table 1.

Screening Visit
Procedures during the screening visit include:

- Written informed consent will be obtained.
- A complete psychiatric and medical history will be acquired.
- The diagnosis of BD and current depression will be confirmed using the Mini International Neuropsychiatric Interview (MINI)
- The severity of depression will be ascertained using the MADRS, and the clinician rated and subject rated Inventory of Depressive Symptoms Scales (IDS-S and IDS-CR).
- The YMRS, Clinical Global Impression – Severity Scale (CGI-S-BD), Hamilton Anxiety Rating Scale (HAM-A) and Mood Disorders Centre Side Effects Scale (MDCSES) will also be administered.
- Information about concomitant medication use will be obtained.
- A physical examination will be performed including: vital signs, weight, hip and waist measurements.
- Subjects with a personal or family history of significant cardiovascular problems or with cardiac abnormalities on physical exam will have an EKG. Laboratory measures will be obtained, including hematology, serum chemistry, liver and kidney function, thyroid function, cholesterol lipid screen, quantative beta Hcg levels (for all females of childbearing age), and urine drug screen.
- Trough (12-hour post-dose) serum lithium or divalproex levels will be obtained in patients taking these medications.
- Blood samples will be collected for genetic and epigenetic testing as well as for measurements of serum and intracellular neurochemicals in patients who have consented to this.
- Patients taking medications not permitted by the study protocol will begin tapering them. The medications must be discontinued within 4 weeks.

Baseline Visit and Randomization

NOTE: The baseline visit is to be conducted within one week after the screening visit

Procedures during the baseline visit include:

- The MADRS, IDS-CR, IDS-S, HAM-A, YMRS, CGI-S-BD, MDCSES, Quality of Life, Enjoyment, and Satisfaction Questionnaire (Q-LES-Q) will be administered
- Information about concomitant medication use will be obtained.
- Vital signs, weight, hip and waist measurements will be taken.
- Patients who continue to meet all inclusion criteria and no exclusion criteria will be prescribed either escitalopram 10 mg daily or bupropion XL 150 mg daily for treatment of their depression. **NOTE:** Patients who are taking lamotrigine or quetiapine plus a mood stabilizer, or patients who are taking quetiapine alone, must have been on these medications for a minimum of 6 weeks prior to starting antidepressant medication.
- Patients not currently taking a mood stabilizer or an SGA will be prescribed one or both at a therapeutic dose

Weeks 2, 4, 6, 8, 10, 12, and 14
At each follow-up visit:

- The MADRS, IDS-CR, IDS-S, HAM-A, YMRS, CGI-S-BD, CGI-Improvement (CGI-I-BD), and MDCSES will be administered.
- Medication adherence will be assessed by patient interview and pill counts.
- Information about concomitant medication use will be obtained
- Vital signs, weight, hip and waist measurements will be taken.
- Trough serum lithium or divalproex levels in patients taking these medications will be obtained as clinically indicated.

Week 16 or Endpoint Visit
The final study visit will occur at week 16, or when the patient has completed at least 4 weeks of treatment, has been in remission that is maintained for $\geq$ 2 weeks and $\leq$ 8 weeks, and elects to enroll in the double-blind phase, or when the patient is withdrawn from the study for any reason.

At the endpoint visit:

- The MADRS, IDS-CR, IDS-S, HAM-A, YMRS, CGI-S-BD, CGI-I-BD, MDCSES, and Q-LES-Q.
- Medication adherence will be assessed by patient interview and pill counts.
- Information about concomitant medication use will be obtained.
- Vital signs, weight, hip and waist measurements will be taken, and a physical examination will be carried out.

- Laboratory investigations including hematology, serum chemistry, liver and kidney function, thyroid function, cholesterol, lipid screen, quantitative beta Hcg levels (for all females of childbearing age), urine drug screen and trough serum lithium or divalproex levels in patients taking these medications will be obtained.
- Blood samples will be collected for genetic and epigenetic testing as well as for measurements of serum and intracellular neurochemicals 2 weeks after criteria for treatment response is met.

Withdrawal Criteria
A patient will be withdrawn from the open-label study phase if:

- s/he experiences a manic or hypomanic episode
- s/he experiences a SAE (see section below on AEs and SAEs)
- s/he is non-adherent with study medication or anti-manic medication(s) (defined as missing ≥ 25% of doses of medication(s) in a 4-week period)
- s/he withdraws consent
- in the opinion of the study psychiatrist, it is in the patient's best interest to be withdrawn from the study

Data Analysis
Analysis of data for the primary and secondary endpoints will be conducted on an intent-to-treat basis, with the last observation carried forward for subjects who do not complete the open-label study phase. All statistical tests will be two-tailed, with a significance level of 0.05.

Primary Outcome
The **primary outcome** for the open-label phase is **mean improvement in MADRS score from baseline to endpoint**. Improvement in MADRS scores will be analyzed using t-tests.

Secondary Outcomes
Secondary outcomes include:

- Improvement in IDS-CR and IDS-S scores
- Improvement in HAM-A scores
- Rates of **response**, defined as ≥ 50% improvement in baseline MADRS score
- Rates of **remission**, defined as a MADRS score ≤ 8 and YMRS score ≤ 8 for ≥ 2 weeks, or a score of ≤ 2 (borderline mentally ill) on the CGI-S- BD for ≥ 2 weeks
- Rates of **treatment-emergent mania and hypomania**, defined as a YMRS score ≥ 16 for hypomania and ≥ 20 for mania at any study visit
- **Overall psychiatric status** and **overall improvement**, using the CGI-S-BD and CGI-I-BD scales
- Rates of **adverse events** (AEs) and **serious adverse events** (SAEs), using the MDCSES
- **Quality of life**, using the Q-LES-Q.

Changes from baseline to endpoint in scores on the MADRS, IDS-CR, IDS-S, HAM-A, YMRS, CGI-S-BD, CGI-I-BD, and Q-LES-Q will be analyzed with t-tests or ANOVA.

Changes from baseline to endpoint on categorical measures, including response and remission rates and rates of adverse events, will be analyzed using Chi-square tests.

Descriptive Statistics
Data on the following demographic and illness variables will also be gathered:

- Age
- Gender
- Ethnicity
- Marital status
- Occupational status
- Treatment location (inpatient versus outpatient)
- Age at onset of illness
- Numbers of previous depressive, manic, and hypomanic episodes
- Length of current depressive episode
- Number of previous trials of antidepressants, mood stabilizers, and second generation antipsychotic medications

DOUBLE-BLIND MAINTENANCE TREATMENT PHASE
Patients who are in remission from their index depression for ≥ 2 weeks and ≤ 8 weeks are eligible to take part in the double-blind maintenance phase. **There are two routes to enter the double-blind phase:**

- following completion of the open-label phase, or
- following a period of clinical treatment, not exceeding 16 weeks, with the same medications used in the open-label phase. In addition, patients who respond to clinical treatment with carbamazepine (serum level 20-50 umol/L) plus an antidepressant may also enter the double-blind phase.

Experimental Design
During the double-blind phase, all patients will continue treatment with their anti-manic medication(s), and will be randomized to one of two treatment arms for up to 52 weeks:

- Patients randomized to the "**8 week arm**" will discontinue antidepressant treatment after 8 weeks, as recommended in current clinical practice guidelines [10]. The antidepressant will be tapered in a double-blind manner beginning at 6 weeks, and will be substituted with placebo by 8 weeks.
- Patients randomized to the "**52 week arm**" will continue treatment with their antidepressant medication for 52 weeks, or until withdrawal from the study.

Allocation to the "8-week" or "52-week" arms will be done in a double-blind manner using a central data centre . Randomization will be stratified in permuted blocks of size 4 based on:

- antidepressant type (escitalopram or bupropion XL)
- anti-manic medication(s)
- study site

At the beginning of the double-blind phase, antidepressant medications and anti-manic medication(s) will be prescribed in the same dose patients received at the end of the open-label phase.

- A reduction in the dose of the study medication (antidepressant or placebo) will be permitted only in the case of intolerable side effects. **The dose of the study medication cannot be increased during the double-blind phase.**
- A reduction in the dose of anti-manic medication(s) will be permitted only in the case of intolerable side effects. In addition, in patients taking lithium, divalproex, or carbamazepine, the dose may be increased or decreased if the serum level falls outside the therapeutic range (see Inclusion and Exclusion Criteria, below).
- **Any change in the dose of study medication, mood stabilizer, or SGA must be documented on the CRF**.

Patients will be assessed every 2 weeks from baseline to week 12, and then monthly until study endpoint, or more frequently if clinically indicated.

Inclusion Criteria
Patients meeting **all** of the following criteria will be eligible to be **included** in the double-blind study phase:

1. Taking escitalopram 10-30 mg/day or bupropion XL 150-450 mg/day, in addition to either a mood stabilizing medication (lithium, serum level 0.6-1.2 mEq/L, divalproex, serum level 350-700 mM or carbamazepine, serum level 20-50 umol/L), an SGA (risperidone 1-6 mg/day; olanzapine 5-30 mg/day; quetiapine IR or XR 150-900 mg/day; aripiprazole 10-30 mg/day; or ziprasidone 80-160 mg/day), two mood stabilizers, a mood stabilizer plus an SGA (including asenapine 5-20 mg/day), or a mood stabilizer or SGA plus lamotrigine (100-400 mg/day).
2. Has adequately tolerated the combination of antidepressant plus mood stabilizer, and is currently in remission for ≥ 2 weeks and ≤ 8 weeks.
3. If female and of childbearing potential, is using an adequate method of contraception.

Exclusion Criteria
Patients meeting **any** of the following criteria will be **excluded** from the double-blind study phase:

1. Has a history of rapid cycling, defined as ≥ 4 mood episodes in the preceding 12 months.
2. Has current manic, hypomanic, or subsyndromal hypomanic symptoms, defined as a YMRS score ≥ 8 at the screening or baseline visits.
3. Has active substance dependence, other than caffeine or nicotine dependence, in the preceding 3 months. Otherwise, patients with comorbid substance abuse or other comorbid psychiatric illnesses will be eligible to participate in the study.
4. Is at high risk for suicide, as defined by a score of ≥ 4 on the suicide item of the MADRS, or in the opinion of the investigator.
5. Has an unstable medical illness, as defined by a change in medication or other treatment in the past 4 weeks, or in the opinion of the investigator.

6. Has significant abnormalities on an electrocardiogram.
7. Is pregnant or lactating.
8. Has experienced an episode of mania, hypomania, or a mixed episode during antidepressant treatment of the acute depression, defined as a YMRS score of ≥ 16 at any open-label study visit, or in the opinion of the study psychiatrist.

Medications and Dosages

Antidepressants
Escitalopram will be prescribed in the dose range 10-30 mg daily.

- In patients randomized to the "8-week group", escitalopram will be tapered, discontinued, and replaced with placebo over a period of 2 weeks, beginning at the week 6 study visit. The tapering schedule for escitalopram is outlined in table 2.
- The dose of escitalopram (or matching placebo) may be decreased in 10 mg increments only in the case of intolerable side effects. The dose must remain within the protocol-defined range of 10-30 mg daily at all time points.

Bupropion XL will be prescribed in the dosage range 150-450 mg daily.

- In patients randomized to the "8-week group", bupropion XL will be tapered, discontinued, and replaced with placebo over a period of 2 weeks, beginning at the week 6 study visit. The tapering schedule for bupropion XL is outlined in table 2.
- The dose of bupropion XL (or matching placebo) may be decreased in 150 mg increments only in the case of intolerable side effects. The dose must remain within the protocol-defined range of 10-30 mg daily at all time points.

Pre-packaged blister packs with unique patient identification numbers will include tapering schedules incorporated, so that regardless of the group to which the patients are assigned, the number and appearance of the tablets will remain constant through the tapering process.

Anti-manic medications
Anti-manic medication doses will remain constant during the double-blind phase. The only exception is in the case of intolerable side effects, or if the serum level of lithium, divalproex, or carbamazepine falls outside of the therapeutic ranges in patients taking these medications.

A blood sample will be drawn to measure serum levels of lithium, divalproex and carbamazepine, in patients taking these medications, at baseline, 24 weeks, endpoint, and at any other time if clinically indicated.

Concomitant Psychiatric Treatments
Concomitant psychiatric medications permitted to control anxiety or insomnia during the double-blind study phase include:

- Lorazepam (maximum dose 4 mg daily)
- Clonazepam (maximum dose 2 mg daily)
- Temazepam (maximum dose 30 mg daily)
- Zopiclone (maximum dose 15 mg daily).

Concomitant Non-Psychiatric Treatments
Patients may continue taking previously prescribed medications used to treat underlying stable organic illnesses. The use of herbal medicines is not permitted.

All concomitant medications must be documented on the Case Report Form. For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition must be documented on the Adverse Event Form of the CRF.

Study Visits and Measures
Procedures for study visits during the maintenance phase are summarized in Table 3.

Patients who were not enrolled in the open-label phase will need to complete the double-blind screening visit. In addition, a 1 page summary from the patient's GP or a copy of the intake assessment will be obtained. The summary or intake assessment should be faxed to the PI prior to randomizing the patient. For patients who completed the open-label study phase, a screening visit is not necessary.

Screening Visit (for patients who were not enrolled in the open-label phase)
Procedures during the screening visit include:

- Written informed consent will be obtained.
- A complete psychiatric and medical history will be acquired.
- The diagnosis of BD and current euthymia will be confirmed using the Mini International Neuropsychiatric Interview (MINI)
- The MADRS, IDS-CR, IDS-S, HAM-A, YMRS, CGI-S-BD, and MDCSES will also be administered.
- A physical examination will be performed including: vital signs, weight, hip and waist measurements.
- Subjects with a personal or family history of significant cardiovascular problems or with cardiac abnormalities on physical exam will have an EKG.Laboratory measures will be obtained, including hematology, serum chemistry, liver and kidney function, thyroid function, cholesterol and lipid screen, quantitative beta Hcg levels (for all females of childbearing age), and urine drug screen.
- Trough (12-hour post-dose) serum lithium,divalproex or carbamazepine levels will be obtained in patients taking these medications.
- Patients taking medications not permitted by the study protocol will begin tapering them. The medications must be discontinued within 4 weeks.

Baseline Visit

> *NOTE: The baseline visit is to be conducted a) within one week after the endpoint visit of the open label phase OR b) for those patients who were not enrolled in the open-label phase, within one week after the screening visit*

At the baseline visit:

- The MADRS, IDS-CR, IDS-S, HAM-A, YMRS, CGI-S-BD, CGI-I-BD, MDCSES, and Q-LES-Q.
- Medication adherence will be assessed by patient interview and pill counts (in patients who completed the open-label phase).
- Information about concomitant medication use will be obtained.
- Vital signs, weight, hip and waist measurements will be taken.
- Neurocognitive Testing will be conducted.
- For premenopausal women participating in nail sampling, phase of the menstrual cycle will be recorded

Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48
Patients will be assessed every two weeks for the first 12 weeks of the double-blind phase, and every 4 weeks therafter.

- The MADRS, IDS-CR, IDS-S, HAM-A, YMRS, CGI-S-BD, CGI-I-BD, and MDCSES will be administered.
- The Q-LES-Q will be administered at week 24.
- Medication adherence will be assessed by patient interview and pill counts.
- Information about concomitant medication use will be obtained
- Vital signs, weight, hip and waist measurements will be taken.
- Laboratory investigations including trough serum lithium, divalproex or carbamazepine levels in patients taking these medications will be obtained at week 24, and as clinically indicated.
- Blood samples will be collected at week 12 for genetic and epigenetic testing as well as for measurements of serum and intracellular neurochemicals in patients who have consented to this.
- Neurocognitive Testing will be conducted only at weeks 10 and 24.
- Nail samples will be collected at weeks 12, 24, and 36. Participants will be asked to trim their nails two weeks prior (to ensure 2 weeks of growth at time of collection)- at weeks 10, 22, 34.
- For premenopausal women participating in nail sampling, phase of the menstrual cycle will be recorded at weeks 10 and 24

Week 52 or Endpoint Visit
The final study visit will occur at week 52, or when the patient is withdrawn from the study for any reason.

At the final visit:

- the MADRS, IDS-CR, IDS-S, HAM-A, YMRS, CGI-S-BD, CGI-I-BD, MDCSES, and Q-LES-Q will be administered.
- Medication adherence will be assessed by patient interview and pill counts.
- Information about concomitant medication use will be obtained
- Vital signs, weight, hip and waist measurements will be taken, and a physical examination will be carried out.
- Laboratory investigations including hematology, serum chemistry, liver and kidney function, thyroid function, cholesterol and lipid screen, quantative beta Hcg levels

(for all females of childbearing age), urine drug screen and trough serum lithium or divalproex levels in patients taking these medications will be obtained.
- Blood samples will be collected for genetic and epigenetic testing as well as for measurements of serum and intracellular neurochemicals in patients who have consented to this.

Withdrawal Criteria
A patient will be withdrawn from the double-blind study phase if:
- s/he reaches a primary endpoint (see below)
- s/he experiences a SAE
- s/he is non-adherent with study medication, mood stabilizer, SGA, or Lamotrigine (defined as missing ≥ 25% of doses of medication(s) in a 4-week period)
- s/he withdraws consent
- in the opinion of the study psychiatrist, it is in the patient's best interest to be withdrawn from the study

Data Analysis

Primary outcome
The **primary outcome** for the double-blind phase is **mean survival time in the study until the occurrence of any mood episode** (manic, hypomanic, or depressive), as determined using Kaplan-Meier survival analysis. A hypomanic episode is defined as a YMRS score ≥ 16, a manic episode as a YMRS score of ≥ 20, and a depressive episode as a MADRS score ≥ 20. **The primary outcome will also be reached in any patient who**
- has a CGI-S-BD of ≥ 4 at any visit
- is hospitalized for a mood episode
- requires additional treatment for a mood episode in the judgment of the study psychiatrist.
- has a MADRS suicide item score ≥ 4 at any visit
- attempts or completes suicide

A Cox proportional hazards model will be used to assess the difference in relapse rates between the "8 week" and "52 week" groups, adjusted for pre-randomization covariates, including drug combination and baseline patient characteristics (e.g. number of previous episodes). This analysis will be intention-to-treat. Patients who do not reach the endpoint will be included in the analysis but will have their event time censored as of the last completed visit.

Secondary outcomes
Secondary outcomes include:
- time to manic or hypomanic episode
- time to depressive episode
- time to study discontinuation for any reason (eg. onset of mood episode, intolerable side effects, patient or clinician decision)

- the percentages of patients who experience any mood episode, a manic or hypomanic episode, or a depressive episode
- the percentage of patients who experience subsyndromal symptoms and the percentage of time spent with subsyndromal symptoms
- rates of adverse events and SAEs
- mean endpoint scores on the clinical rating scales.

Descriptive Statistics
Data on the following demographic and illness variables will be also gathered:

- Age
- Gender
- Ethnicity
- Marital status
- Occupational status
- Treatment location (inpatient versus outpatient)
- Age at onset of illness
- Numbers of previous depressive, manic, and hypomanic episodes
- Length of current depressive episode
- Number of previous trials of antidepressants, mood stabilizers, and second generation antipsychotic medications
- Baseline MADRS, IDS-S, IDS-CR, HAM-A, YMRS, CGI-S-BD, and QLESQ scores

Changes in MADRS, IDS-CR, IDS-S, HAM-A, YMRS, CGI-S-BD, and CGI-I-BD scores will be analyzed using methods for longitudinal data (hierarchical/random effects models). The percentage or number of subjects experiencing mood episodes, depressive episodes, and manic episodes, as well as differences in baseline patient characteristics (severity of depressive episode, number of previous episodes, absence/presence of comorbidity, etc) will be examined using analysis of variance, Kruskal-Wallis tests, or chi-square tests of contingency tables as appropriate. All statistical tests will be two-tailed with a significance level of 0.05.

ADVERSE EVENT REPORTING

Adverse Event (AE) Definition
An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a pharmaceutical product. It does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

This definition includes any occurrence that is new in onset, or aggravated in severity or frequency from the baseline condition. An abnormal result of a diagnostic procedure, including a laboratory test abnormality, is considered an AE if it:

- Results in discontinuation from the study
- Requires treatment or any other therapeutic intervention
- Requires further diagnostic evaluation, excluding a repetition of the same procedure to confirm the abnormality
- Is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Serious Adverse Event (SAE)
Any untoward medical occurrence which:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Hospitalizations due to a relapse of mania or depression will not be considered as SAEs since this is a normal course of the illness and is an expected occurrence.

Any patient who experiences an SAE will be withdrawn from the study. All SAEs must be reported to the Principal Investigator within 24 hours. Medical and scientific judgment will be exercised in deciding whether expedited reporting of AEs other than SAEs is appropriate, for example adverse events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

Unexpected Adverse Event (UAE)
An unexpected adverse event (UAE) is any adverse event, the nature or severity of which is not consistent with the applicable product information, *eg.*, investigator's brochure for an unapproved investigational product, or product monograph for an approved product.

Associated With Use of the Drug(s)
An AE will be considered associated with use of study medication if the attribution is possible, probable or very likely.

Attribution Definitions
Not Related: An AE which is not related to use of the drug(s).

Doubtful: An AE for which an alternative explanation is more likely, *eg.* concomitant drug(s), concomitant disease(s), and / or the relationship in time suggests that a causal relationship is unlikely.

Possible: An AE which may be due to use of the drug(s). An alternative explanation, *eg.* concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable, and therefore the causal relationship cannot be excluded.

Probable: An AE which is likely due to use of the drug(s). The relationship in time is suggestive, *eg*. it is confirmed by de-challenge. An alternative explanation, *eg.* concomitant drug(s), concomitant disease(s)is less likely.

Very Likely: An AE which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, *eg.* concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive, *eg*. it is confirmed by de-challenge and re-challenge.

Procedures
All AE's which occur between the first trial procedure, *ie.* administration of scales after signed consent, and last dose of investigational product administration, will be reported. Those meeting the definition of SAE must be reported within 24 hours using the SAE form.

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document. Wherever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document.

Serious Adverse Events
Patients who experience a SAE will be discontinued from the trial. All SAEs occurring during the course of the trial must be reported within 24 hours to the Principal Investigator. The cause of death of a subject in a clinical trial, regardless of whether the event is expected or presumed to be associated with the investigational agent, is an SAE.

The report must include protocol title, the subject's study initials and date of birth, the subject's unique identification number or medication code number, the period of intake of study medication, nature of the adverse event, and investigator's attribution. All oral reports of an SAE must be confirmed within five days by a written, more detailed report and signed by the local investigator

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until either:

- the event resolves
- the event stabilizes
- the event returns to baseline, if a baseline value is available
- the event can be attributed to a source other than the study drug, or to other than study contact
- one month elapses after the subject's discontinuation from the study.

Pregnancies
Pregnancies occurring after the first intake of the study medication are considered immediately reportable events. They must be reported to the Principal Investigator within

one working day after the investigator has gained knowledge of them, using the Pregnancy Notification Form for Clinical Trials. The subject must immediately be withdrawn from the trial. Follow-up information regarding the outcome of the pregnancy and any potential sequelae in the infant will be required.

Emergency Breaking of the Study Blind

The study blind can be broken at the discretion of the study psychiatrist in exceptional circumstances, for example in the case of a serious adverse event in which knowledge of whether the patient is taking antidepressant or placebo will affect the medical care that the patient receives. If the study psychiatrist breaks the study blind, the reason must be documented in a report forwarded to the principal investigator and the Data Safety and Monitoring Board.

SAMPLE SIZE CALCULATIONS

Based on previous studies, we predict that half of the patients in the "8 week" study arm will experience a relapse of a mood episode. The relapse rates in the "52 week" study arm is unknown. We will power the study to detect a 20% difference in overall relapse rates (i.e, a 50% relapse rate in the "8 week" arm and a 30% relapse rate in the "52 week" arm), as a difference in rates lower than this are unlikely to be clinically significant. A difference of 20% between the groups would mean a number needed to treat (NTT) of 5, that is, one needs to treat 5 patients with the combination to improve outcome in one patient.

Based on one year event rates of 50% and 30% in the 8-week and 52-week arms, respectively, the required sample size for the double-blind study phase is 95 patients per arm if there are no dropouts and 108 patients if the cumulative dropout rate is 25%. Thus the total number of patients that will be recruited to provide 80% power to detect a difference between the two treatment arms on the primary comparison is 216, factoring in a 25% drop-out rate. These calculations are based on the method of Lachin and Foulkes [11].

Table1: Procedures for the Open Label Study Phase

Visit Window: Every 2 weeks : +/- 2 days Every 4 weeks : +/- 4 days	Screening	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16/ Termination
Informed Consent	X									
MINI (5.0.0)	X									
Psychiatric History	X									
Family Psychiatric History	X									
Medical History	X									
Physical Exam	X									X
Lab Tests	X					X				X
EKG	**X									
Genetic/ Neurochemical Blood Samples	X									*X
Vital Signs/Weight	X	X	X	X	X	X	X	X	X	X
Hip/Waist	X	X	X	X	X	X	X	X	X	X
MADRS	X	X	X	X	X	X	X	X	X	X
IDS-CR	X	X	X	X	X	X	X	X	X	X
IDS-S	X	X	X	X	X	X	X	X	X	X
YMRS	X	X	X	X	X	X	X	X	X	X
CGI BP-S	X	X	X	X	X	X	X	X	X	X
CGI BP-I			X	X	X	X	X	X	X	X
MDCSES	X	X	X	X	X	X	X	X	X	X
Q-LES-Q		X								X
HAM-A	X	X	X	X	X	X	X	X	X	X
Medication Count			X	X	X	X	X	X	X	X
Adverse Event		X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X

*Samples will be collected 2 weeks after criteria for treatment response has been met.

**An EKG will be performed on any subject with a personal or family history of significant cardiovascular problems or with cardiac abnormalities on physical exam

Table 2: Discontinuation Schedule for Escitalopram and Bupropion XL in Patients Randomized to the "8-week" Study Arm

	Week 6	**Week 7**	**Week 8**
Escitalopram			
30 mg daily	20 mg daily	10 mg daily	STOP
20 mg daily	10 mg daily	10 mg daily	STOP
10 mg daily	10 mg daily	10 mg daily	STOP
Bupropion XL			
450 mg daily	300 mg daily	150 mg daily	STOP
300 mg daily	150 mg daily	150 mg daily	STOP
150 mg daily	150 mg daily	150 mg daily	STOP

Table 3: Procedures for Double-Blind Study Phase

Order medications

	Screening	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52/ Termination
Informed Consent	X																	
Psychiatric History	X																	
MINI (5.0.0)	X																	
Family Psychiatric History	X																	
Medical History	X																	
Physical Exam	X																	X
EKG****	X																	
Lab Tests	X										X							X
Genetic/ Neurochemical Blood Samples	X							X										X
Vital Signs/ Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hip/Waist	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MADRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IDS-CR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IDS-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
YMRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-BP-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-BP-I		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MDCSES	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Q-LES-Q		X									X							X
HAM-A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Count		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cognitive Testing		X					X				X							
Nail Samples**								X			X			X				
Phase of Menstrual Cycle***		X					X				X							

*Screening visit omitted for those participants who enter through the Open Label Phase

** Participant needs to trim nails 2 weeks prior to sample collection*** For premenopausal women participating in nail sampling only
**** An EKG will be performed on any subject with a personal or family history of significant cardiovascular problems or with cardiac abnormalities on physical exam

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