Prevention of Relapse and Recurrence of Bipolar Type I Depression: A Study Protocol for a Multi-site Randomized, Double-blind, Placebo-substitution Trial

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Abstract

Background: Bipolar (BP) I disorder affects 1.6% of the US adult population and results in estimated healthcare costs of $40 billion annually. It is characterized by a predominance of major depressive episodes interspersed with manic and hypomanic episodes. Most current practice guidelines are based upon expert consensus and generally recommend using mood stabilizer monotherapy for initial treatment of BP I depression, while avoiding antidepressants and using only mood stabilizer monotherapy for prevention of relapse and recurrence of depression. We hypothesize that long-term mood stabilizer plus antidepressant therapy will result in fewer depressive relapses and recurrences versus mood stabilizer monotherapy.

Methods/design: 200 patients with BP I depression will receive initial lithium plus fluoxetine therapy for 12 weeks. Responders will be randomized to double-blind maintenance therapy with either: (i) lithium plus fluoxetine, or (ii) lithium monotherapy (following fluoxetine taper and discontinuation) for an additional 50 weeks. The primary outcome is the proportion of subjects in each condition who have a depressive relapse or recurrence during maintenance therapy. Depressive relapse or recurrence is defined as a return of moderate depressive symptoms.

Discussion: We believe that evidence-based medicine will eventually support the use of concurrent antidepressant therapy for prevention of depressive relapse and recurrence in patients with BP I disorder. The paucity of modern controlled clinical trials studying the best method for preventing depressive relapse and recurrence of BP I disorder has led to contradictory practice guidelines and confusion as to the best treatment for BP I disorder. This study seeks to determine whether subjects who respond to initial mood stabilizer plus antidepressant therapy will have a superior long-term efficacy and fewer depressive relapses and recurrences if they continue therapy with maintenance mood stabilizer plus antidepressant therapy versus mood stabilizer therapy alone.

Trial registration: ClinicalTrials.gov Trials Register - NCT00961961.

Keywords: Bipolar disorder; Manic-depression; Antidepressant; Lithium; Fluoxetine; Major depression; Relapse prevention

Background

BP I disorder is characterized by a preponderance of MDEs with a life-time prevalence of at least one manic episode of abnormally elevated, expansive, or irritable mood lasting at least 1 week (or any duration of hospitalization). In addition, ‘mixed’ manic and depressive, and hypomanic episodes (lasting ≥ 4 days) may also occur. BP I disorder is diagnostically stable over time [6,7], and may be genetically and biologically distinct from BP type II disorder which lacks manic episodes [8-10]. Although there is a growing awareness of the prevalence of BP disorder in the US, the public health implications of this disorder have only recently been recognized [11,12]. In part, this is the result of under-recognition of BP disorder [8].

Specific Aims and Hypotheses

The primary study aim is to examine if long-term therapy with combined lithium plus fluoxetine results in a lower relapse and recurrence rate of MDEs versus lithium monotherapy following recovery from BP I MDE (as defined by DSM-IV-TR criteria.) We hypothesize that long-term lithium plus fluoxetine therapy will result in lower relapse and recurrence rates versus lithium therapy alone.

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in fewer MDE relapses (within 6 months) and recurrences (after 6 months) versus lithium monotherapy. The secondary study aim is to compare the relative safety, tolerability, and frequency of syndromal and sub-syndromal manic, hypomanic, and mixed manic and depressive episodes during long-term treatment with combined lithium plus fluoxetine therapy versus lithium monotherapy following recovery from acute MDE. We hypothesize that lithium plus fluoxetine therapy will result in a similar frequency of syndromal and sub-syndromal mood conversion episodes, and a similar frequency of treatment-emergent adverse events. We further hypothesize that lithium plus fluoxetine therapy will result in fewer suicide ideation events and fewer study discontinuations versus lithium monotherapy.

Methods/Design

Study design

This is a 2-site, randomized, double-blind, placebo-substitution, parallel group study of the safety, tolerability, and efficacy of combined lithium plus fluoxetine therapy vs. lithium monotherapy during long-term treatment of BP I disorder.

A total of 200 subjects will be enrolled. The study consists of 3 phases. Phase I is an 8-week, initial treatment with combined lithium plus fluoxetine therapy. Phase IIa is a 2-week consolidation period during which remitted patients with a 17-item Hamilton Rating Scale for Depression (HRSD) [13] score ≤ 8 continue on initial therapy. Phase IIb is a 2-week double-blind taper phase during which patients are randomized to either: (i) continue initial lithium plus fluoxetine therapy, or (ii) taper and discontinue fluoxetine therapy with a placebo substitution. Phase III is a 50-week, double-blind, parallel group comparison of combined lithium plus fluoxetine versus lithium monotherapy.

Study population

Subjects will be recruited from established resources at the Penn and Rush investigative sites; Table 1 displays the study inclusion and exclusion criteria, source of study materials, and role of study personnel.

Subject recruitment

Subjects will be recruited without regard to gender, race, or ethnicity, provided that they meet all study inclusion criteria and do not meet study exclusion criteria. Women who are pregnant or breast-feeding will not be included in the trial. Minors younger than 18 years old will not be included in the trial, as the proposed therapies in the trial are not currently approved for use in the treatment of MDE in children. Subjects at both sites will be recruited from the local outpatient psychiatry clinics, family practice clinics, and from institutional review board (IRB)-approved advertisements.

Randomization and stratification procedures

Blocked randomization with randomly varying block sizes will be performed. This will be accomplished in two stages, within strata defined by gender and history of substance abuse disorder (yes/no). First, a block size will be randomly selected from a small set of possible block sizes. The group numbers will then be randomly permuted within that block. This procedure will be continued until we have randomized 50 subjects within each treatment condition. We will generate random numbers and permute the numbers within each block using the random number generator and user written code in Stata statistical software (Stata Corp., College Station, Tex.).

Study drug

We will select fluoxetine for this study based upon preliminary work by our group and others showing a favorable safety and tolerability profile and low manic switch rate during initial and maintenance therapy in BP I and BP II MDE [14-20]. Fluoxetine will also be chosen for its long elimination half-life and low risk of discontinuation syndrome [21-23]. We will select lithium as the ‘gold standard’ mood stabilizer because of its well established safety and efficacy profile in BP I disorder [7,19,20,24].

In study phase I (i.e., acute treatment), we will utilize a dose escalation design of fluoxetine from 10-80 mg daily with a dose titration schedule based upon symptom reduction as determined by the HRSD score ≤10 by week 8, and a final HRSD score ≤ 8 by week 12. This design is consistent with FDA labeling for fluoxetine, and on its safety profile in prior BP disorder studies [7,19,20]. The dose of lithium

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**Table 1: Inclusion criteria and source document.**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Source</th>
<th>Assessor*</th>
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</thead>
<tbody>
<tr>
<td>Age ≥ 18 years</td>
<td>Self-report</td>
<td>1,3</td>
</tr>
<tr>
<td>DSM IV Axis I BP I disorder, current DSM IV Axis I MDE.</td>
<td>Structured Clinical Interview for DSM-IV (SCID)</td>
<td>1,2,4</td>
</tr>
<tr>
<td>HRSD - 17 item score ≥ 16</td>
<td>Hamilton Rating Scale for Depression</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>YMRS score ≤ 12</td>
<td>Young Mania Rating Scale</td>
<td>1,2,3,4</td>
</tr>
<tr>
<td>Clinical Global Impression rating ≥ 4 (≥ ‘moderate’)</td>
<td>Clinical Global Impression (CGI)</td>
<td>1,2,4</td>
</tr>
<tr>
<td>No current alcohol or drug abuse or dependence within 3 months</td>
<td>Baseline visit</td>
<td>1,2,4</td>
</tr>
<tr>
<td>Ability to provide daily data for prospective NIMH Life Charting.</td>
<td>Baseline visit</td>
<td>1,2,4</td>
</tr>
<tr>
<td>No contraindication or prior sensitivity to treatment with fluoxetine or lithium</td>
<td>Baseline visit</td>
<td>1,2,4</td>
</tr>
<tr>
<td>No uncontrolled medical condition (e.g., hepato-renal, cardiovascular, endocrine, metabolic disease)</td>
<td>Baseline visit</td>
<td>1,2,4</td>
</tr>
<tr>
<td>No pregnant or nursing women or women of child-bearing potential unwilling to use contraception</td>
<td>Baseline visit</td>
<td>1,2,4</td>
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<tr>
<td>Not actively suicidal, psychotic, or requiring hospitalization</td>
<td>Baseline visit</td>
<td>1,2,4</td>
</tr>
<tr>
<td>Not using medication contraindicated with lithium or that may interfere with measurement of lithium levels</td>
<td>Baseline visit</td>
<td>1,2,4</td>
</tr>
<tr>
<td>Not using hypericum, L-tryptophan, or s-adenosylmethionine</td>
<td>Baseline visit</td>
<td>1,2,4</td>
</tr>
<tr>
<td>No presence of apparent secondary gain (e.g., court-ordered treatment)</td>
<td>Baseline visit</td>
<td>1</td>
</tr>
<tr>
<td>Able to participate in a 62-week study</td>
<td>Baseline visit</td>
<td>1,3</td>
</tr>
<tr>
<td>Final, overall eligibility</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

* Because there are different roles for specific study personnel at each investigative site, the following will indicate the personnel involved in each study procedure: 1. Study nurse or Physician assistant; 2. Physician sub-investigator; 3. Study coordinator; 4. Principal investigator.
Study drug blinding procedure

Study drug to be used in this trial will be commercially available and have established safety profiles. Fluoxetine 10 mg and 20 mg capsules will be precisely measured to determine the ‘best fit’ for over-encapsulation in the smallest stock gelatin capsule shell that will accommodate them without altering the shape of the capsules. Capsule shells will be certified contaminant-free and BSE-free, and will be hand-filled and inspected by a licensed pharmacist for accuracy. Capsule shells will then be back-filled and lightly packed with pharmacetical-grade lactose monohydrate USP powder verified for purity with a current Certificate of Analysis. Capsule shells will then be sealed, dusted with sodium chloride to remove outside traces of powder, then packaged, sealed and assigned an internal Investigational Drug Service (IDS) lot number for each batch of product.

Placebo capsules will be prepared in a similar fashion as fluoxetine capsules, using identical gelatin over-encapsulation shells. A lactose monohydrate NF (Spectrum Quality Products, Inc., New Brunswick, NJ) tablet will be packed into the capsule shell to give a similar appearance and ‘feel’ to the active fluoxetine capsule.

Treatment procedures

To assure uniform treatment, clinical management will be conducted in a structured fashion [25]. Subjects will be treated by an experienced clinician who is familiar with the use of fluoxetine and lithium. While formal re-constructive psychotherapy will be prohibited, supportive therapy and limited advice-giving will be encouraged, along with general medication management. Sessions will typically last 30-45 minutes, although the initial session may take up to 3 hours. The principal investigator at each site will oversee the pharmacotherapy and provide supervision to co-investigators. Adverse events will be monitored at each study visit and remedied as clinically warranted. A study doctor will be available on a 24-hour basis by emergency phone service and pager for medical emergencies. Subjects will be instructed to immediately call the study doctor if they have adverse events or a worsening of their condition. They will be instructed to return to the study site for an unscheduled study visit for further evaluation. Given this level of close clinical monitoring, it is anticipated that worsening affective symptoms will be detected in a timely fashion.

Subjects, who have an adverse event that, in the study doctor’s opinion, would warrant discontinuing treatment, will be discontinued from the trial. In this case, blinded conditions will be discontinued and the subject will be treated as clinically warranted. Subjects will be instructed to adhere to all study procedures. Subjects will be instructed to return all unused study drug at each study visit. A capsule count will be conducted at each study visit to monitor compliance. Subjects will be queried about any deviations from the prescribed dosing regimen. Subjects who have not taken at least 75% of the prescribed medication dose during any study period will be designated as non-compliant. Subjects who show ‘non-compliance’ during two study periods will be considered for early discontinuation from the trial.

A blinded study coordinator will dispense the properly coded study drug to the subject with accompanying instructions containing a 24-hour emergency telephone number. Subjects and study raters will be blinded to the fluoxetine treatment condition. However, drug codes will be maintained at the IDS, at each study site for emergency un-blinding.

Accurate capsule counts and dosage records will be maintained by the study coordinator.

Study drug administration procedures

Lithium dosing will start at 600 mg daily for one week. A serum lithium level will be obtained after one week of therapy. Based upon response, tolerability, and a lithium level of 0.8-1.5 mEq/L, the dose of lithium may be increased to 900 mg daily for the second week of therapy. Another lithium level will be obtained after one week of therapy at 900 mg daily. Based upon response, tolerability, and a lithium level of 0.8-1.5 mEq/L, the dose of lithium may again be increased to 1200 mg daily during week 3 of therapy. This process will be repeated until a lithium level of 0.8-1.5 mEq/L is achieved. We anticipate that the majority of subjects will attain a therapeutic lithium dose and lithium level by week 4 of therapy. Lithium may be increased to a maximum of 2100 mg daily by week 6 (based upon tolerability and lithium level). Lithium will then be maintained at the maximum tolerated dose for the remainder of the trial. Lithium may be administered on a once or twice daily basis up to 900 mg daily, and on a twice daily basis at doses >900 mg daily. Subjects who are unable to tolerate a minimum dose of 300 mg daily, or who do not achieve a minimum lithium level of 0.8 mEq/L will be discontinued from the trial (unless documented by the investigator with an explanation of the deviation from the minimum lithium dose and/or lithium level). To maintain steady state lithium levels of 0.8-1.5 mEq/L, levels will be drawn as close to 12 hours as possible after the last oral dose of lithium. Subjects taking lithium once daily in the evening will be instructed to take their dose as close to 12 hours as possible prior to having the level drawn. Subjects taking lithium on a twice daily basis who have a morning appointment will be instructed to take their evening dose as close to 12 hours as possible prior to the morning study visit, and not to take their morning lithium dose until the level has been drawn. Similarly, subjects taking lithium on a twice daily basis who have an evening appointment will be instructed to take their morning dose as close to 12 hours as possible before their evening study visit, and not to take their evening lithium dose until after the level is drawn. This degree of lithium level monitoring is standard procedure at both investigative sites, and has resulted in lithium dosing within a ‘therapeutic window’ with minimum ‘physiologic drift’ in levels.

Fluoxetine dosing will be initiated at 10-20 mg daily during the first week of treatment. The dose may then be increased by 10 or 20 mg every week as tolerated to a maximum of 80 mg daily by week 4 of treatment. This dose will be maintained for the next 4 weeks of treatment. The fluoxetine dose may be reduced to a minimum of 10 mg daily based upon response and tolerability. Fluoxetine will be administered on a once or twice daily basis. Subjects unable to tolerate fluoxetine 10 mg daily will be discontinued from the trial, and treated as clinically warranted.

Diagnostic and Clinical Outcome Measures

(i) Structured Clinical Interview for DSM-IV (SCID) [26] will serve as the primary instrument for diagnostic case ascertainment.

(ii) Hamilton Rating Scale for Depression (HRSD) scale [13] is a validated, clinician-rated instrument that ascertains depressive symptom severity. It is consistent across racial and ethnic groups [27]. It will serve as the primary outcome measure.

(iii) Life Chart Method (LCM-P) [28] will be used to ascertain syndromal and sub-syndromal mood conversion episodes over time. The LCM-P is a subject-rated diary that elicits prospective
information on mood, function, sleep, co-morbid symptoms, menstrual cycle, medication compliance, drug dosage, and life events. It tracks sub-syndromal mood events that may go unnoticed. It will serve as a secondary outcome measure.

(iv) Hypomania Interview Guide (including Hypothymia) (HIGH-C) [29] will be used to prospectively elicit hypomanic episodes. The HIGH-C is a semi-structured, clinician-rated instrument that is validated against other mania scales [30]. It will serve as a secondary outcome measure.

(v) Clinical Global Impressions – BP Version (CGI-BP) [31] is a clinician-rated measure of global symptom severity (CGI/S) and symptom change (CGI/C). It will serve as a secondary outcome measure.

(vi) Young Mania Rating Scale (YMRS) [30] is a validated, clinician-rated instrument that ascertains the presence and severity of mild to severe manic symptoms. It will serve as a secondary outcome measure.

(vii) Self Rating Mania Scale (SRMS) [32] is a subject-rated measure of manic symptoms that has been widely used in BP trials and has been validated against the YMRS [32]. It will serve as a secondary outcome measure.

(viii) Quality of Life Inventory (QLI) [33] is a patient-rated measure of satisfaction with key domains of daily life. It is widely used [34] and performs across racial populations [35]. It measures both satisfaction responses and their importance to the subject. It will serve as a secondary outcome measure.

(ix) Treatment Emergent Symptom Side Effect (TESS) [36] rating is a clinician-rated profile of AEs that occur during the trial. The TESS includes the date of onset and cessation, severity (i.e., mild, moderate, severe), relationship to treatment (i.e., none, possible, probable, definite), and outcome (i.e., none, dosage change, study termination). TESS data will be obtained by spontaneous patient report, doctor query, and changes in physical and laboratory findings. Adverse events will be recorded in accordance with the Consolidated Good Clinical Practice Guidelines of the US Department of Health and Human Services [37]. Adverse events will be reported to the respective IRB and to the Data and Safety Monitoring Board members for review. It will serve as a secondary outcome measure.

(x) Columbia Suicide History Form (CSHF) and Severity Rating Scale (CSSRS) [38] are validated, clinician-rated instruments that ascertain past and current suicide risk, ideation, and behavior. They will serve as secondary outcome measures.

### Outcome Criteria and Disposition

‘Response’ will be defined as a final HRSD score ≤ 10 plus a CGI/S score of 1, 2, or 3, plus no longer meeting DSM IV MDE criteria by week 8 (study visit 7). Subjects must also have a final YMRS score ≤ 12 and not meet DSM IV criteria for mania by the LCM-P, HIGH-C, or SRMS rating, and must not be actively suicidal by the CSSRS rating. ‘Non-response’ will be defined as a HRSD score >10, or a CGI/S score ≥ 4, or a final YMRS score >12, or meets criteria for mania or sub-syndromal mania by the LCM-P, HIGH-C, or SRMS rating, or is actively suicidal by the CSSRS. Subjects meeting criteria for non-response will be discontinued from the trial and treated as clinically warranted.

### Study Phase Procedures

#### Phase I procedures

Visit 1 (Week 0) will be an intake evaluation to determine subject eligibility.

Initial subject contact will be made via telephone triage. General information about referral source, subject demographics, clinical variables (e.g., duration of current episode, current treatment, medical disorders), and the presence of suicidal ideation will be obtained. A brief description of the study procedures will be provided, and the subject will be provided with an appointment for an intake visit. At the intake appointment, informed consent and initial clinical data will be obtained. A complete psychiatric evaluation and medical history will be obtained, along with a physical examination and laboratory evaluation (including drug screen and electrocardiogram). Any subject with abnormal laboratory results that may constitute a meaningful co-morbid medical illness will be excluded from the trial. Subjects will also have clinical and QOL outcome ratings performed.

Visit 2 (Week 1) will be a baseline visit. At the baseline visit, the study informed consent will be reviewed and signed, and all questions will be answered. Clinical ratings will confirm study eligibility. Subjects will then start the fluoxetine plus lithium therapy (as described above).

Visits 3-7 (Weeks 1-8) will be the period during which open-label fluoxetine plus lithium therapy is maximized with lithium 300–2100 mg daily (and lithium levels of 0.8-1.5 mEq/L) plus fluoxetine 10-80 mg daily. Subjects will have follow up study visits at week 1, 2, 4, 6, and 8. The following outcome measures will be obtained at each study visit: HRSD, LCM-P, YMRS, HIGH-C, CGI/S, CGI/C, SRMS, CSSRS, TESS, vital signs, weight, concomitant medications, and dosage record. Capsule counts will be maintained to enhance compliance. The QLI will be obtained at baseline and week 8 (or at study termination). Serum lithium levels will be obtained at study visits 3, 4, 5, 6 (optional), and 7. Additional serum lithium levels may be obtained as clinically warranted (Table 2).

<table>
<thead>
<tr>
<th>Baseline</th>
<th>V3, W1</th>
<th>V4, W2</th>
<th>V5, W 4</th>
<th>V6, W 6</th>
<th>V 7, W 8</th>
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<tbody>
<tr>
<td>HRSD</td>
<td>X</td>
<td>X</td>
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<td>Quality of Life</td>
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<td>Dosage, Con Meds</td>
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<td>X</td>
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<tr>
<td>Vital Signs, Weight</td>
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<td>X</td>
<td></td>
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<tr>
<td>Laboratory Pharmcogenetic</td>
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<tr>
<td>Lithium Level</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X (opt)</td>
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</tr>
</tbody>
</table>

**Table 2**: Phase I study procedures.
Study phase IIa procedures

Visit 8 (Week 10) will be an open-label, 2-week consolidation phase during which subjects who responded during study phase I continue on their established lithium plus fluoxetine dosages. Subjects will return for follow up study visit at week 10. The following outcome measures will be obtained at this study visit: HRSD, LCM-P, YMRS, HIGH-C, SRMS, CGI/S, CGI/C, TESS, CSSRS, vital signs, weight, dosage record, concomitant medications, and capsule count. ‘Response’ in study phase IIa will be defined as a HRSD score ≤ 8 plus a CGI/S score of 1, 2, or 3, no longer meeting DSM IV MDE criteria, and a final YMRS score ≤ 12, not meeting criteria for mania or sub-syndromal mania according to the LCM-P, HIGH-C, or SRMS rating, and not actively suicidal via the CSSRS rating. ‘Non-response’ is defined as a HRSD score > 8, or a CGI/S score ≥ 4, or meeting MDE criteria, or a YMRS score > 12, or meeting criteria for mania or subsyndromal mania by the LCM-P, HIGH-C, or SRMS ratings, or is actively suicidal by the HRSD and CSSRS ratings.

Study phase IIb procedures

Visit 9 (Week 12) will be a 2-week, randomized, double-blind fluoxetine taper / discontinuation phase. Subjects will return for follow up week 12. Subjects will continue to take their established lithium dose for the 2 week period, and will be randomly assigned to either: (i) continue established fluoxetine dose for 2 weeks, or (ii) taper and discontinue fluoxetine over 2 weeks. The fluoxetine dose will be gradually reduced by 10-20 mg every 3-7 days (depending upon the established fluoxetine dose). The following outcome measures will be obtained: HRSD, LCM-P, YMRS, HIGH-C, SRMS, CGI/S, CGI/C, CSSRS, TESS, vital signs, weight, dosage record, and concomitant medications. Capsule counts will be maintained (Table 3). ‘Response’ in study phase IIb will be as a HRSD score ≤ 8 plus a CGI/S score of 1, 2, or 3, and no longer meeting MDE criteria. Subjects must also have a final YMRS score ≤ 12 and not meet criteria for mania or sub-syndromal mania according to the LCM-P, HIGH-C, or SRMS ratings. Subjects must not be actively suicidal via the HRSD or CSSRS ratings. Non-response is defined as a HRSD score > 8, or a CGI/S score ≥ 4, or meeting MDE criteria, or a YMRS score > 12, or meeting criteria for mania or subsyndromal mania by the LCM-P, HIGH-C, or SRMS ratings, or is actively suicidal by the HRSD and CSSRS ratings.

Study phase III procedures

Visits 10-17 (Weeks 12–62) will be a 50-week, double-blind, placebo-substitution comparison of lithium plus fluoxetine versus lithium plus placebo in preventing relapse and recurrence of BP I MDE in subjects who have responded to initial therapy. Subjects in study phase III will return for follow up study visits at weeks 14, 16, 20, 26, 34, 42, 50, and 62. The following outcome measures will be obtained at each study visit: HRSD, CGI/S, CGI/C, LCM-P, YMRS, HIGH-C, SRMS, CSSRS, TESS, vital signs, weight, dosage record, concomitant medications, and capsule counts. The QLI will be obtained at study visit 14 and 17 (or at early treatment discontinuation). Laboratory tests will be repeated at study visits 14 and 17 (or at early discontinuation). Lithium levels will be obtained at study visits 10 (optional) and visits 14-17. Unscheduled visits can occur at any time (as clinically warranted). Subjects will be instructed to immediately contact the study doctor if they experience depressive or manic symptoms, or if they have a change in their normal mood state occurring for at least 3 consecutive days. If a change has occurred, the subject will be instructed to return to the clinic for an unscheduled visit for further evaluation (Table 4).

Rescue Therapy

Rescue therapy will be permitted during all study phases in order to: (i) abort sub-syndromal mood conversions deemed to warrant intervention to prevent a syndromal episode; (ii) treat full syndromal episode; and, (iii) manage symptoms that may destabilize recovery (e.g., insomnia, anxiety, agitation). Rescue therapy will also provide a mechanism whereby a subject may receive ‘standard’ intervention, while maintaining data control for variables that may normally occur in a BP population. Attempts will be made to stabilize subjects under these rescue strategies and keep them in the study for follow up visits. Optimizing the dose of lithium or fluoxetine/placebo will be the primary rescue intervention. Rescue therapy will include: (i) change in open-label or double-blind fluoxetine dose (e.g., increase or decrease dose for depressive or manic symptoms); (ii) increase lithium dose to maximize lithium level ≤ 1.5 mEq/L; (iii) adjunctive zolpidem 5-10 mg, zaleplon 5-20 mg, or ramelteon 8 mg for insomnia; and, (iv) adjunctive

<table>
<thead>
<tr>
<th>Table 3: Phase IIa and IIb study procedures.</th>
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<tbody>
<tr>
<td>V8, W 10</td>
</tr>
<tr>
<td>HRSD, CGI/S, CGI/C YMRS, SRMS, HIGH-C</td>
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<tr>
<td>LCM-P, CSSRS, TESS</td>
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<tr>
<td>Dosage Record, Con Meds</td>
</tr>
<tr>
<td>Vital Signs and Weight</td>
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<td>Lithium Level, Laboratory</td>
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</table>

<table>
<thead>
<tr>
<th>Table 4: Phase III study procedures.</th>
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<tbody>
<tr>
<td>HRSD, CGI/S, CGI/C</td>
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<tr>
<td>YMRS, SRMS, HIGH, LCM</td>
</tr>
<tr>
<td>CSSRS, TESS</td>
</tr>
<tr>
<td>Quality of Life</td>
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<tr>
<td>Dosage, Con Meds</td>
</tr>
<tr>
<td>Vital signs &amp; Weight</td>
</tr>
<tr>
<td>Lithium Level</td>
</tr>
</tbody>
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lorazepam 0.5-2.0 mg daily for hypomanic or mixed manic symptoms; (v) adjunctive olanzapine 2.5-20 mg daily or ziprasidone 40-160 mg daily for hypomanic or mixed manic symptoms. Subjects who respond to rescue therapy and no longer meet criteria for syndromal or sub-syndromal manic, hypomanic, or mixed episodes as determined by the LCM-P, HIGH-C, or SRMS rating, will continue in the trial on their newly established therapy. Subjects who do not respond to rescue therapy, become actively suicidal (as determined by the CSSRS), or who are at maximum allowable dose of study drug, will be discontinued from the trial and treated as clinically warranted.

**Primary and Secondary Outcomes**

Primary outcome will be the proportion of subjects in each treatment condition who have a MDE relapse (<6 months) or recurrence (≥ 6 months) during maintenance therapy. Depressive relapse or recurrence is defined as a HRSD score ≥ 14 or a CGI/S score ≥ 4, plus meet DSM IV MDE criteria.

Secondary outcomes will include the proportion of subjects in each condition with the following: (i) manic episode according to the LCM-P, HIGH-C, or SRMS ratings that meet criteria of ≥ 7 days with functional impairment (e.g., agitation, risk taking, hospitalization) or a YMRS score ≥ 16; (ii) hypomanic episode according to the LCM-P, HIGH-C, or SRMS rating meeting criteria of ≥ 4 days without functional impairment; (iii) mixed manic episode according to the LCM-P, HIGH-C, or SRMS rating meeting criteria for mania or hypomania plus a HRSD score ≥ 14 or a CGI/S score ≥ 4; (iv) sub-syndromal mania according to the LCM-P, HIGH-C, or SRMS ratings with symptoms not meeting DSM IV criteria (i.e., without functional impairment), or a total YMRS score <16, or manic symptoms lasting <7 days, or hospitalization; (v) sub-syndromal hypomania according to the LCM-P, HIGH-C, or SRMS ratings not meeting DSM IV criteria (e.g., hypomania <4 days); (vi) sub-syndromal mixed episode as determined by the LCM-P, HIGH-C, SRMS, and HRSD ratings not meeting DSM IV criteria for mixed manic episode (e.g., brief mixed episode <7 days); (vii) sub-syndromal depressive episode according to the LCM-P and HRSD rating not meeting DSM IV criteria for MDE (e.g., episode <14 days or HRSD score <14); (viii) time to first manic or sub-syndromal episode; (ix) time to onset of first MDE relapse or recurrence; (x) time to first intervention for manic, depressive, or sub-syndromal episode; (xi) early discontinuation from the study; (xii) mean change from baseline for total HRSD, YMRS, CGI/S, CGI/C, QLQ; (xiii) adverse events; and; (xiv) change in suicidal ideation as determined by the HRSD and CSSRS ratings. The HIGH-C and LCM-P will be used to ascertain and confirm daily symptoms and time to first onset of mood conversion and rescue therapy.

**Statistical Procedures**

**Overview**

The primary aim of this study will test the hypothesis that long-term lithium plus fluoxetine therapy will result in a lower MDE relapse and recurrence rate versus lithium monotherapy in BP I disorder subjects who have recovered from an MDE. The primary outcome measure will be relapse or recurrence of MDE in study phase III. A secondary aim of the study will test the hypothesis that combined lithium plus fluoxetine therapy will result in fewer study discontinuations, fewer suicidal ideation events, and a similar frequency of syndromal and sub-syndromal conversion episodes versus lithium monotherapy. The treatment conditions will be compared on the proportion of subjects who survive in each treatment condition (i.e., no MDE relapse or recurrence) by week 50 of study phase III. Secondary outcome measures will include frequency of manic, hypomanic, and mixed episodes, sub-syndromal manic, hypomanic, mixed manic and depressive events, time to onset of each event, time to first rescue intervention, and rates of AEs and early study discontinuation. For overall analysis, the data will be pooled across sites. We will conduct additional analyses that assess differences between investigative sites to ensure that any differences observed are comparable between the two sites.

**Power estimates and sample size determination**

The sample sizes required in study phase III will depend on the response and discontinuation rates in study phases I and II. Thus, it is anticipated that each site will enroll 100 BP I MDE patients (or 26 patients per year) into study phase I. This sample size will provide us with sufficient power (n=100) to test our primary hypothesis in study phase III. We anticipate a total of 100 subjects randomized in study phase III, or 50 patients per treatment condition. We believe that this sample size has sufficient power to test our primary hypothesis of equality of relapse or recurrence rates between treatment conditions. With a sample size of 50 per group, we will have 94% power to detect a difference between treatment conditions at the 0.05 level using a 2-sided Fisher’s Exact test, assuming the percentage of subjects who have no relapse or recurrence by 50 weeks is 32% on lithium vs. 68% on lithium plus fluoxetine. Table 5 displays the power available to detect significant differences between treatment conditions at the end of study phase III, assuming several relapse and recurrence rates (Table 5).

Support for these relapse rates during lithium therapy was derived from the analysis of Altshuler et al. [39] who observed relapse rates of 68% for MS monotherapy vs. 32% for MS plus AD therapy. Moreover, patients who continued AD therapy at least 6 months following recovery from MDE were less likely to suffer a relapse vs. patients who stopped AD therapy prior to 6 months (p=0.02) [39].

**Statistical plan for analysis of outcomes**

Descriptive analyses will be described for each treatment condition including frequency (or categorical variables), mean, median, range, Standard Deviation (SD), Standard Error of the Mean (SEM) for continuous variables, and 95% confidence of the medians (for skewed distributions). In addition, the percentage of subjects with treatment emergent adverse events will be compared using the Fisher’s Exact test. Discontinuation rates due to adverse events, lack of efficacy, and other reasons for study discontinuation will also be analyzed using these tests.

After conducting preliminary descriptive analyses, primary and secondary outcome analyses will be performed. The primary outcome is relapse or recurrence (yes/no) of MDE as measured from entry into study phase III. The primary hypothesis of equality of relapse or recurrence rates between treatment conditions will be tested using a two-sided Fisher’s Exact test.

**Table 5: Power to detect significant differences in relapse/recurrence rates among treatment groups.**

<table>
<thead>
<tr>
<th></th>
<th>Lithium Monotherapy</th>
<th>Lithium plus Fluoxetine</th>
<th>Power*</th>
</tr>
</thead>
<tbody>
<tr>
<td>32%</td>
<td>68%</td>
<td>32%</td>
<td>94%</td>
</tr>
<tr>
<td>38.7%</td>
<td>68%</td>
<td>38.7%</td>
<td>80%</td>
</tr>
<tr>
<td>31%</td>
<td>60%</td>
<td>31%</td>
<td>80%</td>
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<tr>
<td>65%</td>
<td>90%</td>
<td>65%</td>
<td>82%</td>
</tr>
<tr>
<td>5%</td>
<td>36%</td>
<td>5%</td>
<td>97%</td>
</tr>
<tr>
<td>5%</td>
<td>26.5%</td>
<td>5%</td>
<td>80%</td>
</tr>
</tbody>
</table>

* Group sizes of n=50 using Fisher’s Exact test with significance =0.05
Survival analyses will also be performed to compare the median time to MDE relapse or recurrence between treatment conditions. Kaplan-Meier product-limit estimates of the survivor functions (probability of survival from relapse over time) for each condition will also be obtained, and a graph of the estimated probabilities of survival for each treatment condition versus time will be assessed. In these analyses, we will use the log-rank test of equality of these survivor functions. Cox proportional hazards modeling will be used to compare the hazards for MDE relapse between the two conditions. Cox proportional hazard analyses will allow for assessment of relative risk for MDE relapse for the two treatment conditions, while also adjusting for other potential correlates of relapse including various demographic and clinical factors, as well as lithium levels. It will also allow stratification on study site, if appropriate. We will use graphical checks as implemented in Stata to assess the critical assumption of proportionality of the hazard ratios for these models.

Analysis of secondary aims

Manic and hypomanic episodes (yes/no), sub-syndromal hypomanic and mixed hypomanic and depressive episodes (yes/no), including time to onset will also be measured in all study phases. To examine these, we will use an approach based on the Fisher’s Exact test (to compare rates between treatment groups) and survival analysis (to compare the median time to occurrence). We will conduct an analysis in which the outcome is time to event or MDE relapse/reurrence, whichever occurs first. This will allow us to assess the outcomes of MDE and mood conversion events jointly.

Exploratory analyses will be conducted that compare the proportion of subjects who have hypomania between treatment conditions using Fisher’s Exact test and will compare the median time to develop hypomania using the log-rank test. We will apply the Wilcoxon rank sum test to compare the median number of syndromal and sub-syndromal events per subject between treatment conditions in each study phase.

Secondary analyses will also implement survival analysis to compare time to first syndromal and sub-syndromal event between conditions in each study phase. Kaplan-Meier curves will be constructed to compare the survival curves between treatment conditions. In addition, the log rank test will be applied to test the hypothesis of equality of the survival curves between treatment groups.

Moderator and mediator analyses will also be conducted (e.g., number of prior MDEs, gender, age, rapid cycling status, and number of prior medication courses). We will test whether these variables may be a moderator variable by including each variable and a treatment group by variable interaction term into our Cox regression models.

Missing data

Missing values for outcomes will not be imputed for the primary test of efficacy. The statistical methods to be used have the advantage of allowing for a variable number of observations per subject. For example, the primary hypotheses will be tested according to the intent to treat principle, which treats subjects who dropped out as having had a relapse or recurrence. The characteristics of subjects with incomplete data at randomization will also be examined. However, there will be limited statistical power to detect small differences between subjects with and without complete follow-up data. To assess the potential bias introduced by differential withdrawal among treatment groups, a comparison of withdrawal rates and/or time to withdrawal will be included as an ancillary analysis.

Type 1 errors

Due to the large number of comparisons in the secondary analyses, it is possible that chance alone may cause rejection of the null hypothesis for one or more outcome variables that actually do not differ significantly. We consider adjustment for such multiple comparisons to be unduly conservative because the traditional adjustment for multiple comparisons, the Bonferroni method, assumes that the various tests are statistically independent. In fact, it is likely that the various outcome measures from this study will be highly correlated with each other. To determine whether this is indeed the case, we will construct correlation matrices between the different continuous measurements at each time point, to determine if the outcomes are significantly and positively correlated. Results of statistical tests will also be assessed, to determine if they are consistent with common sense and with each other. An isolated finding of one measurement between treatment conditions will be interpreted cautiously. In contrast, group differences for multiple measures will lend clinical, as well as statistical, support to the conclusions. It is important to note that the primary aim of efficacy for this trial is based on one statistical test, with the other tests being conducted as secondary analyses. Any reports stemming from this project will inform the reader whether the results they describe were obtained as part of the primary or the secondary analyses of the trial.

Site differences

Site comparability in treatment and rater reliability will be rigorously maintained. To assess whether any important differences may exist by site, secondary and descriptive analyses will be conducted that replicate the analyses of the trial, but are stratified by site. Although we anticipate that the significance level of the statistical tests will change due to the reduced power to detect possible site differences between conditions, these stratified analyses will be important to assess whether the direction and magnitude of differences is similar between conditions, and whether subjects at each site are comparable with regard to basic demographics. Indicator variables for the two sites will be included in the generalized estimating equations analyses.

Site by covariate interactions may be explored, e.g. a site x treatment interaction term may be included in the regression models if the descriptive analyses suggest that one treatment is more effective at a particular site.

Data and safety monitoring

Data and Safety Monitoring Board (DSMB): In order to assess changes in risk / benefit ratio to study subjects and to obtain independent oversight of the study conduct, an external Data and Safety Monitoring Board (DSMB) will be established to oversee the progress of the study. External DSMB study reviews will be conducted at 6-month intervals. The DSMB members will review and monitor the study procedures, potential risks, changes in risk/benefit ratio, subject enrollment, number and nature of adverse events, and any study-related serious adverse events (SAEs). All SAEs will be reviewed by the DSMB members in order to determine whether additional safety measures should be initiated, or whether there is a change in the risk / benefit ratio for study subjects.

Adverse event monitoring and documentation: Information on adverse events will be obtained by several methods: (i) spontaneous subject reports; (ii) clinician-elicited reports; and, (iii) changes in laboratory and physical findings. An adverse event will be defined as any untoward medical or non-medical occurrence that arises after the subject has provided informed consent, irrespective of a causal relationship to the treatment or study procedure. Lack of treatment
efficacy will not be defined as an adverse event, whereas symptom worsening may be described as an adverse event. All adverse events will be listed on the TESS profile. All adverse events will be monitored and/or treated until resolved. If clinically significant laboratory changes occur, these changes will be reported as adverse events. They will be evaluated and monitored until they have resolved. All SAEs or life-threatening adverse events will be promptly reported to the IRB and the DSMB.

Data monitoring: A project manager trained in regulatory procedures and experienced in managing clinical and research documentation will be responsible for maintaining the completeness of all source documentation and case report forms (CRFs). A study and database manager will verify the accuracy of data recorded on the CRFs in the subject study binder and identify any discrepancies and inconsistencies. Study quality assurance and the data checking process will take place in a continuous fashion to maintain the integrity of the data.

Discussion

Patients with BP I disorder spend a disproportionate amount of time in the depressive phase of their illness. Poor functional outcome in BP disorder is more highly correlated with the depressive, rather than the manic, phase [40-42]. These observations support the need for developing new strategies for treating and preventing BP I MDE relapse and recurrence. While most attention has focused on the development of anti-manic therapies, the greatest challenge to clinicians is the management of recurrent BP MDE [43]. Diagnostic uncertainty [44,45], limited MS efficacy [44,45], and concern over AD-induced mania [44-48] make the management of BP I MDE a challenge. Early in the illness course, severe and protracted MDEs often follow a briefer manic or hypomanic episode. As the illness progresses, however, the MDEs occur with greater frequency and longer duration [49].

Eventually, MDEs dominate the clinical picture, ultimately resulting in treatment-resistant BP MDE [50]. The predominance of BP I MDE with its attendant disability burden [42] suggests that new therapeutic efforts be directed toward treating and preventing BP I MDE. Current practice guidelines for BP I MDE are often contradictory [5,51-55], and there are few controlled trials available to substantiate the validity of these guidelines. Most practice guidelines for treating BP MDE recommend initial mood stabilizer therapy and avoiding antidepressant medication (or limiting it to the lowest effective dose for the shortest period of time necessary.) However, these guidelines have not been prospectively tested. A recent 18-month, placebo-controlled trial of lamotrigine versus lithium monotherapy examined the time to relapse or recurrence of depressive and manic episodes after remission from an acute BP MDE found that depressive occurrences were 3-times more frequent than manic, and that the proportion of patients who remained depression-free for 12 months was not significantly different for lamotrigine (57%) or lithium (46%) versus placebo (45%) [56].

Conclusion

In conclusion, this study will seek to address some of the scientific questions regarding long-term treatment for prevention of relapse and recurrence of BP I MDE.

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Conflict of Interest Disclosures

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References