



Department of Psychiatry

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SUSTAINING REMISSION OF PSYCHOTIC DEPRESSION

PROTOCOL & DATA ANALYTIC PLAN

Project Summary-----	2
Specific Aims-----	3
Research Strategy	
- Significance-----	4
- Innovation-----	5
- Progress report on STOP-PD-----	6
- Research design and methods-----	7
- Data analysis-----	13
Protection of Human Subjects	
- Leadership plan to protect the integrity of subject data-----	16
- Risks to subjects-----	21
- Adequacy of protection against risks-----	24
- Potential benefits-----	27
- Importance of knowledge to be gained-----	27
- Data and safety monitoring board-----	28
Inclusion of Women and Minorities-----	28
Resource Sharing-----	29
Bibliography-----	31
Appendix 1: Pharmacotherapy Protocol-----	39

1. PROJECT SUMMARY

Psychotic depression (PD) is a severe disabling disorder with considerable morbidity and mortality. Between 19% and 45% of inpatients with major depression have psychotic features, with greater prevalence in older patients. Although electroconvulsive therapy has well-established efficacy in the treatment of PD, its use is limited by several factors. As a result, the pharmacologic treatment of PD is common. Expert guidelines recommend the combination of antidepressant and antipsychotic medications in the pharmacologic treatment of PD. The recently completed Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) was the first NIMH-funded randomized controlled trial (RCT) to examine the efficacy and tolerability of newer antidepressant and antipsychotic medications in the acute treatment of younger and older persons with PD. The combination of sertraline and olanzapine was significantly more efficacious than olanzapine combined with placebo. Both treatments were equally well tolerated, but were associated with clinically significant weight gain and elevation of lipids. Older persons, however, had significantly less weight gain than younger persons.

Little is known about the continuation treatment of PD. Of particular concern, it is not known whether antipsychotic medication needs to be continued once an episode of PD responds to pharmacotherapy. This issue has profound clinical relevance. On the one hand, the unnecessary continuation of antipsychotic medication exposes a patient to adverse effects, such as weight gain and metabolic disturbance. On the other hand, premature discontinuation of antipsychotic medication has the potential risk of early relapse of a severe disorder. The primary goal of this Renewal application, therefore, is to assess the risks versus benefits of continuing olanzapine in younger and older patients with PD, once the episode of depression has responded to treatment with sertraline and olanzapine. This goal will be addressed through a 36-week double-blind RCT, in which placebo is substituted for olanzapine in half the study group, following a period of sustained remission. We hypothesize that sertraline+olanzapine will be more efficacious than sertraline+placebo in preventing relapse of PD. This study provides the unique opportunity to systematically assess the effect of antipsychotic discontinuation (as opposed to switching from one antipsychotic to another) on olanzapine-related weight gain and metabolic disturbance. Additional innovative aims of the study are to examine age and genetic polymorphisms as predictors/moderators of treatment variability, potentially leading to more personalized treatment of PD, and to employ population pharmacokinetics to determine the magnitude and consistency of exposure to study drugs. Olanzapine is selected because it is the only atypical antipsychotic with established efficacy and tolerability in the treatment of both younger and older adults with PD. This research will be transformative, by providing clinicians with a much-needed evidence base to guide the continuation treatment of one of the most disabling and lethal psychiatric disorders.

2. SPECIFIC AIMS

2.1 INTRODUCTION TO STUDY AIMS: Major depression with psychotic features (psychotic depression; PD) is a severe disorder associated with considerable morbidity and mortality.¹ Although ECT has well-established efficacy as a treatment for PD,^{2,3} its use is limited by several factors: a high rate of relapse following completion of ECT,^{4,5} lower rates of response in non-academic centers,⁶ significant disparities in its availability,⁷ and the fact that many patients prefer pharmacologic treatment, because they find the concept of ECT and the potential side effect of cognitive impairment unacceptable. Because of these limitations, the pharmacologic treatment of PD is common.⁸ Expert guidelines recommend the combination of antidepressant and antipsychotic medications as an alternative to ECT in the treatment of PD.^{9,10} The recently completed Study of the Pharmacotherapy of Psychotic Depression (STOP-PD)¹¹, which involved collaboration of the current group of principal investigators, was the first NIMH-funded RCT to examine the efficacy and tolerability of combination therapy using newer antidepressant and antipsychotic medications in the acute treatment of PD. The combination of sertraline and olanzapine was significantly more efficacious than olanzapine monotherapy, and the two treatments had comparable tolerability.¹¹ Nevertheless, both treatments were associated with increases in weight and lipids over the 12-week study.¹¹

Once an episode of major depression responds to antidepressant medication, the antidepressant must be continued to prevent relapse.¹² However, it is not known whether antipsychotic medication needs to be continued once an episode of PD has responded to combined antidepressant-antipsychotic treatment. This issue is of profound clinical importance. On the one hand, the unnecessary continuation of antipsychotic medication exposes a patient to adverse effects, some of which have considerable public health significance. On the other hand, premature discontinuation of antipsychotic medication has the potential risk of early relapse of a severe, disabling disorder. The main goal of this collaborative Renewal Application, therefore, is to assess the benefits and risks of continuing olanzapine in older and younger persons with PD, once the episode of depression has responded to treatment with sertraline and olanzapine. This goal will be addressed through a RCT, in which placebo is substituted for olanzapine in half the study group, following a period of sustained remission. Specifically, we propose a three-phase study. In the Acute Phase, participants will receive open-label sertraline and olanzapine for a maximum of 12 weeks. Subjects who respond to treatment will enter the Stabilization Phase, where they will continue to receive open-label sertraline and olanzapine for an additional 8 weeks. Participants who meet remission criteria will then be randomized to 36 weeks of double-blind treatment with either sertraline+olanzapine or sertraline+placebo.

2.2 PRIMARY AIM

Aim 1: Assess the efficacy of olanzapine, in combination with sertraline, in preventing relapse of psychotic depression

H1: The combination of sertraline and olanzapine will be associated with less risk of relapse than the combination of sertraline and placebo

2.3. SECONDARY AIMS

Aim 2: Assess the effect of continuation versus discontinuation of olanzapine on weight and metabolic variables in remitted psychotic depression

H2: The combination of sertraline and olanzapine will be associated with higher weight, higher total cholesterol, and higher triglycerides compared with the combination of sertraline and placebo in the randomized phase

Aim 3: Assess the effect of age on olanzapine-associated weight gain in the acute and stabilization treatment of psychotic depression (open-label phase of the study)

H3: Older age will be associated with less weight gain during the open-label phase

2.4 EXPLORATORY AIMS

Aim 4. Explore older age as a moderator of change in weight and metabolic variables during the randomized phase

Aim 5. Explore the association of selected genetic polymorphisms with: i) response, ii) relapse, and iii) weight and metabolic variables during the open-label and randomized phases of the study

3. RESEARCH STRATEGY **SIGNIFICANCE**

3.1 PD is a severe, disabling disorder with considerable morbidity and mortality.^{1,13} 15-20% of persons with major depression have a lifetime history of psychotic features.^{14,15} 19-45% of inpatients with major depression have psychosis, with older depressed persons at greatest risk of PD.^{16,17} PD has been associated with more severe symptoms, slower recovery, greater risk of relapse and recurrence, greater frequency of psychiatric hospitalizations, more psychosocial impairment, higher all-cause mortality, and (in some studies) a higher frequency of suicide than non-psychotic depression (non-PD).^{13,18-21}

3.2 The Acute Pharmacologic Treatment of PD. Several studies have found that PD has better response to a combination of antidepressant and antipsychotic medications, than to either medication alone.¹¹ For the most part, these studies used older generation antidepressant and antipsychotic medications. These findings resulted in practice guidelines recommending combination treatment as the pharmacologic treatment of choice for the acute treatment of PD.^{9,10} Following the availability of SSRI and SNRI antidepressants, a single group of investigators reported a high rate of response of PD to monotherapy with SSRIs and venlafaxine, based on 3 separate RCTs.²²⁻²⁴ The findings of these studies are, however, limited by the fact that none included a placebo-control group, and they lacked a validated measure of psychosis, raising the possibility that persons with non-delusional ideation may have been inadvertently included in the studies.²⁵ Also, these findings have not been replicated in studies by other groups of investigators.²⁶⁻²⁸ Thus, the efficacy of SSRI and SNRI monotherapy to treat PD is uncertain, and combined antidepressant-antipsychotic medication remains the pharmacologic treatment for PD that is recommended by expert guidelines.

3.3 Longer Term Treatment of PD: The Conundrum. Little is known about the continuation and maintenance treatment of PD. Once an episode of major depression responds to antidepressant medication, the antidepressant needs to be continued to prevent relapse and recurrence of depression.^{12,29,30} However, it is not known whether antipsychotic medication needs to be continued once an episode of PD has responded to combined antidepressant-antipsychotic treatment. On the one hand, premature discontinuation of antipsychotic medication has the potential risk of relapse of a severe, disabling disorder. On the other hand, the unnecessary continuation of antipsychotic medication exposes a patient to potential adverse effects. The two sides of this very significant clinical conundrum will now be discussed.

3.4 Relapse of PD. Naturalistic observational studies of PD report relapse rates of 17%-50% (mean=30%) over 12-months of follow-up.³¹⁻³⁶ Studies that have specifically examined the frequency of relapse of PD following a course of ECT have, with one exception, found 12-month rates of 35-50%, despite adequate continuation pharmacotherapy.³⁷⁻⁴⁰ The high rate of relapse after the discontinuation of ECT, and the lack of clarity regarding optimal continuation treatment following ECT, underscores the importance of examining pharmacologic approaches to the longer-term treatment of PD.

There are few data on the relation between discontinuation of antipsychotic medication and relapse of PD. In a chart review of persons with PD who had responded to pharmacotherapy, Aronson et al.³² found that approximately 35% of relapses occurred following the discontinuation of antipsychotic medication in persons who continued to take antidepressant medication; the 3 months after antipsychotic discontinuation was the period of greatest risk of relapse. The only prospective study of antipsychotic discontinuation in PD found a frequency of relapse of 27% over 8 months in 30 mid-life adults who had recovered with combined fluoxetine and perphenazine;⁴¹ the findings of this single study are, however, limited by its open and uncontrolled design, the relatively small number of patients, and the absence of older patients who, based on studies of non-PD,⁴² may conceivably be at greater risk of relapse.

Finally, a few uncontrolled studies have examined relapse in persons with PD who are maintained on the treatment to which they responded.^{39,43,44} In contrast with the aforementioned findings, relapse rates in these studies range from only 0% to 6% over 12 months. Although the findings of these studies are limited by relatively small numbers of patients and uncontrolled design, they suggest a low risk of relapse in patients with PD who are maintained on the treatment regimen that was associated with response.

3.5 Atypical Antipsychotics in the Treatment of PD: Choice of Olanzapine. Atypical antipsychotics have become the first-line treatment of psychosis. Olanzapine is the only atypical with RCT-evidence of efficacy and tolerability in the treatment of both younger and older persons with PD.^{11,45} In STOP-PD, only 5% of participants withdrew from the 12-week study because of side effects.¹ Nevertheless, olanzapine is associated with weight gain and metabolic effects.^{11,46} Our choice of olanzapine for the proposed study is based on careful consideration of alternative atypical antipsychotics that have less severe metabolic effects but do not have documented efficacy for the treatment of PD. Without evidence, efficacy of other atypical antipsychotics in PD

cannot be assumed; for example, olanzapine has been found to be more effective than other atypicals in several RCTs of the treatment of schizophrenia.⁴⁷⁻⁵¹ Each atypical antipsychotic has a number of adverse effects, some of which are potentially problematic in the treatment of PD, especially in older patients.⁵²⁻⁵⁴ Although aripiprazole and ziprasidone have a low incidence of clinically significant weight gain and metabolic dysregulation,^{52,53} there are few data on the efficacy, tolerability, and safety of these drugs in older persons.⁵⁴ Ziprasidone's potential for QTc interval prolongation is a potential concern in older persons with cardiac disease⁵⁴ and would potentially result in the exclusion of many older patients who would otherwise be eligible for the study. Both ziprasidone and aripiprazole are associated with activation and insomnia,⁵²⁻⁵⁴ and in the case of aripiprazole, akathisia and nausea.⁵²⁻⁵⁴ In a recent open-label pilot study of combined aripiprazole and citalopram in 16 younger adults with PD, 63% of participants developed akathisia on a mean daily aripiprazole dose of 14.4 ± 5.5 mg.⁵⁵ The tolerability of aripiprazole and ziprasidone in persons with agitation (a frequent symptom of PD) is unclear. In addition, patients with PD are at high risk of attempted and completed suicide.^{20,21} It is unknown whether the activating effects of aripiprazole and ziprasidone, especially when given in combination with an SSRI, would increase the risk of suicidality in persons with PD. In light of the efficacy of the sertraline/olanzapine combination in STOP-PD,¹¹ and the good overall tolerability and safety of this treatment,¹¹ we have chosen to continue to study this regimen rather than simply assuming that a different antidepressant-antipsychotic combination would be comparably efficacious and better tolerated in younger and older patients. Finally, olanzapine accounts for 25% of sales of atypical antipsychotics in the United States and 30% of sales worldwide.⁵⁶ These figures have remained constant over the past 4 years.⁵⁶ This ongoing, widespread use of olanzapine, despite its known metabolic effects, underscores the importance of the proposed study, to provide patients and clinicians with the best available evidence about the risks and benefits of discontinuing this medication in the long-term treatment of PD.

3.6 Personalizing the Treatment of PD: Pharmacogenetic Considerations. As with other psychiatric disorders, the pharmacologic treatment of PD is associated with considerable treatment variability.⁸ Pharmacogenetic findings have the potential to result in more personalized treatment and possibly preventive strategies. Because the number of individuals recruited to a clinical trial is insufficient to conduct a genome-wide association study,⁵⁷ we will use a candidate-gene approach to explore the following important issues:

- 1) Genetic predictors of relapse of either mood disorders or primary psychotic disorders are currently unknown. We will therefore explore this issue in relation to the proposed study. We assume that the withdrawal of olanzapine will remove pharmacologic antagonism of principally D2 and 5HT2A postsynaptic receptors; the synaptic system will then adapt using autoreceptor mechanisms that might include 5HT1A.⁵⁸⁻⁶⁰ We therefore hypothesize that the genes producing these receptors will be of primary interest as potentially involved in relapse of PD following discontinuation of olanzapine. Of note, the 5HT1A -1019 C/G polymorphism has been implicated in vulnerability to both depression and psychosis,^{61,62} and the Taq1A and -141ins/del polymorphisms of the D2 gene have been associated with vulnerability to psychosis.⁶³
- 2) Several genetic polymorphisms (5HT2C -759C/T, 5HTTLPR s allele, SNAP 25, Leptin -2584 A/G, ADR α 2a -1291C/G, INSIG2) have been associated with antipsychotic-related weight gain.⁶⁴⁻⁷⁷ However, it is not known whether these polymorphisms predict reversal of weight gain following discontinuation of the antipsychotic. We will explore this important issue.
- 3) There have been no published studies of the pharmacogenetics of response or remission in PD. We will therefore explore whether genetic polymorphisms that have been associated with antidepressant response in non-PD (5HTTLPR s and lg alleles, 5HT2A -1438G/A, FKBP5, CRHR1)⁷⁸⁻⁸⁶ and antipsychotic response (D2 -141 ins/del and Taq1A, D3 ser9gly, SNAP 25) and weight gain in schizophrenia^{64-77,87-93} pertain to PD.

Finally, it is important to note that we will participate in the NIMH Human Genetics Initiative so that cell lines, DNA, and genetic data from this very well characterized sample will be available to the wider scientific community. For example, there is emerging evidence that certain genes (e.g. DISC1,⁹⁴ CACNA1C⁹⁵) may confer risk for severe psychiatric illness, as opposed to specific disorders. The genetic data from our study will provide scientists with the unique opportunity to include persons with psychotic depression in analyses pertaining to these 'susceptibility genes'.

INNOVATION

3.7 In addition to being transformative, the proposed research is innovative in several important ways:

- By focusing on PD, this study provides the unique opportunity to assess the effect of antipsychotic discontinuation (as opposed to switching from one antipsychotic to another, which is the case in studies of schizophrenia) on treatment-associated weight gain and metabolic disturbance;

- The study is unique in its inclusion of both younger and older adults. This novel approach will allow us to address age-related questions pertaining to treatment variability;
- An innovative aspect of the design is to include persons in the RCT who have achieved ‘near-remission’ of depressive symptoms. This will allow us to examine whether substantial, but not complete, resolution of depressive symptoms in PD increases the risk of relapse following discontinuation of antipsychotic medication,
- Studying genetic predictors of relapse of PD will be highly innovative. Moreover, this will be the first study to examine whether genetic polymorphisms that predict antipsychotic-related weight gain also predict weight loss following antipsychotic discontinuation;
- Population pharmacokinetics will be used to evaluate drug exposure, which will allow for a more informed and sophisticated interpretation of the study’s findings;
- This study will continue work started in STOP-PD in developing innovative assessment instruments, such as the Delusion Assessment Scale,⁹⁶ in this population. During the course of STOP-PD, we developed the Resolution of Delusions Scale (RODS) to evaluate change in a person’s insight, as a delusion resolves with treatment. In the proposed study, we will assess the psychometric properties of the RODS. If metrics are acceptable, we will use the RODS in exploratory analyses to determine to what extent insight into the prior delusional belief is associated with stability of remission and risk of relapse;
- A novel feature of the assessment is the use of a behavioral sign-based measure of psychomotor function (the ‘CORE’⁹⁷) to examine the effect of psychomotor change, which is common in PD, on treatment outcome;
- If the proposed study is funded, we are committed to promptly submitting a competing supplement that will have a cognitive neuroscience focus, integrating neuropsychology and neuroimaging, to study the relationships between age, brain function, and course of PD.

APPROACH

3.8 PROGRESS REPORT ON STOP-PD (Dates of Award: 6/1/2002-5/31/2007).

STOP-PD was a 12-week double-blind RCT that compared the efficacy, tolerability, and safety of olanzapine plus sertraline (‘combination therapy’) with olanzapine plus placebo (‘olanzapine monotherapy’) in younger and older persons with major depressive disorder and delusions ± hallucinations. The study addressed the following hypotheses: 1) combined olanzapine and sertraline would be more efficacious than combined olanzapine and placebo; 2) the younger age group would have a higher rate of remission than the older age group; 3) treatment would be less well tolerated by older than younger participants. Full details of this study are reported in Arch Gen Psychiatry 2009;66 (8):838-47.¹¹ To summarize:

- The study’s recruitment goal was met, with 259 patients randomized to treatment (n=142 ≥60 years and n=117 <60 years) (Cornell: n=56; Massachusetts: n=59; Pittsburgh: n=63; Toronto: n=81).
- Combination therapy was associated with a higher remission rate over the trial than olanzapine monotherapy (OR=1.28, 95% CI =1.12-1.47, p<.001). 41.9% of randomized combination participants were in remission at their last assessment compared to 23.9% of olanzapine monotherapy participants ($\chi^2_1=9.53$, p=0.002; NNT=5.6). Of the participants who completed 12 weeks of treatment, the remission rate was 66.7% with combined treatment versus 49.2% with monotherapy ($\chi^2_1=4.4$, p=0.036; NNT=5.7).
- Younger and older participants did not differ in rate of remission (OR=1.05, 95% CI=0.80-1.37, p=0.75).
- There was no significant difference between age groups in overall tolerability of treatment or in extrapyramidal side effect scores. Both age groups had statistically significant increases in weight, cholesterol, and triglycerides. Of note, older subjects had significantly less weight gain than younger subjects (7.3 ± 10.3 lbs versus 13.9 ± 4.0 lbs respectively; $F_{1,226}=14.51$, p=0.0002). A statistically significant increase in fasting plasma glucose levels occurred in younger subjects only (mean change of 8.4 ± 41.3 mg/dL from a mean baseline of 93.6 ± 20.4 mg/dL, $t_{211}=2.65$, p=0.009). Only 5% of participants withdrew from the study because of adverse effects.

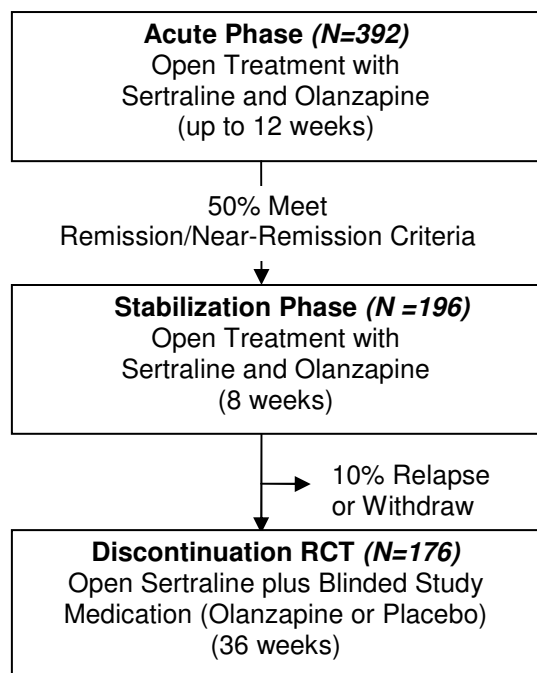
Unpublished Pilot Data from STOP-PD that is Relevant to the Proposed Study:

- As an unfunded pilot project, blood was obtained at week 12/termination in a sub-set of participants (n=66 young and n=102 old) for future pharmacokinetic analyses. Since younger and older groups differed in weight gain, we used population pharmacokinetics to explore whether younger and older groups differed in: i) variability of exposure, which could indicate poorer adherence with olanzapine in one group versus the other [105,106], and ii) magnitude of exposure. Younger and older groups did not differ in either variability (0.98±0.27 vs. 0.96±0.30; $t_{166}=0.36$, p=0.72) or magnitude (1128.9±737.6ug/mL^h vs. 1027.1±477.6ug/mL^h; unequal variances $t_{102}=1.0$, p=.32) of exposure, suggesting that the age-related difference in weight gain was not explained by exposure. The proposed study will examine drug exposure in all participants.

• Participants who were in remission with either combination therapy or olanzapine monotherapy at the completion of STOP-PD were invited to participate in a 3-month double-blind stabilization phase, during which they continued their acute phase treatment. The stabilization phase was designed to collect pilot data on: i) the stability of remission, and ii) the course of side effects. 74 persons (n=29 young and n=45 old) participated in this phase. Of the 48 patients who experienced remission with combination treatment, 10.4% subsequently had a relapse of major depression, psychosis, or both. Participants continued to gain weight in the stabilization phase, but at a slower rate than during STOP-PD (approximately 1.5 lbs/month in stabilization, compared with 4.4 lbs/month in STOP-PD). Tests of fixed effects for changes in metabolic variables during the 6 months of both STOP-PD and the stabilization phase found a statistically significant age x time effect for glucose ($F_{3,149}=3.16, p<0.03$), and trends in age x time effects for triglycerides ($p=0.08$), total cholesterol ($p=0.07$), and LDL cholesterol ($p=0.09$). The younger remitters experienced more of an increase in these metabolic variables than the older remitters. Thus, whereas there was no significant difference between age groups in elevations of glucose and lipids by the end of STOP-PD, differences started to emerge after 6 months of treatment. This suggests that older age may moderate olanzapine-associated metabolic dysfunction, but that this effect may not be apparent until later in the course of treatment. Thus, Aim 3, which pertains to the acute/stabilization phases of treatment (which the majority of participants are expected to complete within 16 weeks), hypothesizes that older age will moderate weight gain only, whereas Aim 4, which pertains to the longer-term treatment of PD, explores whether older age moderates change in both weight *and* metabolic variables.

3.9 RESEARCH DESIGN AND METHODS

Figure 1: Study Design & Subject Flow



3.9.1 General Overview. 392 patients (n=196 aged 18-59 years and n=196 aged ≥60 years) with non-bipolar major depression with psychotic features (delusions, with or without hallucinations) will be enrolled, across 4 sites, in open-label treatment with the combination of sertraline (target dose of 150 mg/day) and olanzapine (target dose of 15 mg/day). Participants who no longer have delusions and hallucinations and either a) have a 17-item Hamilton Depression Rating Scale (HAM-D)⁹⁸ score of ≤10 for 2 consecutive assessments ('full-remission'), or b) are rated 'very much improved' or 'much improved' on the Clinical Global Impression (CGI) Scale⁹⁹ and have a HAM-D score of 11-15 and have ≥50% reduction in the baseline HAM-D score during the last two assessments of the Acute Phase ('near-remission') will continue with open-label sertraline and olanzapine for an 8-week stabilization phase. The acute phase of the study will last a maximum of 12 weeks, but participants will enter the stabilization phase as soon as they meet full-remission criteria. Participants who continue to meet full-remission or near-remission criteria and who have a Mini-Mental State Examination (MMSE)¹⁰⁰ score ≥24 at the end of the stabilization phase will enter the 36-week double-blind, placebo-controlled olanzapine discontinuation phase ('the RCT').

Participants in full-remission or near-remission at the end of the stabilization phase who have a MMSE total score below 24 may be allowed to enter the RCT when specifically approved on a case-by-case basis by the Study's Steering Committee, if the steering committee believes that the lower MMSE score is not caused by clinically significant cognitive impairment and the participant is capable of giving informed consent to participate in the RCT. Participants who achieved near-remission at the end of the Acute Phase and who have a Ham-D score >15 but no delusions or hallucinations at the Week 8 stabilization visit can have two additional weekly stabilization visits. These visits will be used to determine whether the increase in HAM-D score above the partial remission cut-off was transient and ensure that two consecutive weeks of partial remission criteria are met prior to entry in to the RCT. The Steering Committee must discuss and agree to this extension. If the Ham-D score does not return to ≤15 at each of the two additional stabilization visits, the participant will not be eligible to enter the RCT.

Participants will be randomized to either continue olanzapine or to switch from olanzapine to placebo following a 4-week placebo-controlled taper of the olanzapine. All participants will take open-label sertraline for the

duration of the RCT. Randomization will be stratified according to age group (18-59 years and 60 years or older) and stabilization phase outcome ('full-remission' versus 'near-remission'). Relapse is the primary outcome. Participants who experience a relapse will be immediately referred to a designated psychiatrist at the research site, who is not affiliated with the study, for clinical management.

3.9.2 Participant Recruitment and Flow

Overview: Recruitment will begin after 4 months of start-up time and will extend for 38 months (to the end of month 6 of Year 04). The RCT will begin in month 8 of Year 01 and extend 47 months (to the end of month 7 of Year 05). The final 5 months of Year 05 will be used for the completion of data cleaning, data analyses, and write-up of results.

Figure 2: Study Time Line

4-months start-up	51-month Acute, Stabilization, & RCT phases (Including 38 months recruitment)	5-months analysis & write-up
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Recruitment into Open-Label Acute Phase: This study will use the same methods of recruitment and at the same study sites that were successfully used in STOP-PD.¹¹ In addition, we will systematically screen at sites that are affiliated with the study's academic centers, some of which are community settings. Individuals at these affiliate sites who are eligible for, and consent to, the study will then participate in the study at the primary academic center. This approach will facilitate target enrollment and will extend generalizability of the study's findings by recruiting persons from 'less academically-oriented settings'. Entry criteria (see Section 4.2.1) will be the same as those used in STOP-PD which achieved its recruitment goal. Given that the acute phase of the proposed study will use open-label combination treatment, we anticipate that more patients will agree to participate in the proposed study compared with STOP-PD where participants had a 50:50 chance of being randomized to olanzapine plus placebo. Based on 38 months of recruitment, the recruitment goal equates to an average 2.6 participants enrolled per site per month.

Enrollment in the Stabilization and RCT Phases: In the double-blind combination treatment arm of STOP-PD, 63/129 (48.8%) participants who were randomized to combination treatment met remission criteria at some point during treatment, based on the criterion of a Schedule for Affective Disorders and Schizophrenia (SADS)¹⁰¹ delusion item score of 1 ('definitely not delusional') and a minimum of 2 consecutive assessments of a 17-item HAM-D score ≤ 10 . In addition, 10/129 (7.8%) combination treatment participants had the absence of delusions, a CGI improvement score of 'very much' or 'much' improved, and a 17-item HAM-D score of 11-15. Thus, 56.6% of participants who were randomized to combination treatment experienced remission of delusions and remission or substantial improvement of depressive symptoms. Given that treatment in the acute phase of the proposed study will be open-label, we anticipate that remission/near-remission will be higher and drop-out due to withdrawal of consent will be lower than under the double-blind, placebo-controlled conditions of STOP-PD.¹¹ We therefore predict that 60% of participants in the proposed study will achieve remission of psychosis and either remission or substantial improvement in depressive symptoms, allowing them to proceed to the stabilization phase. Nevertheless, we plan to recruit 392 patients to the acute phase of the study, which will facilitate reaching our target recruitment to the RCT should remission plus near-remission in the acute phase be as low as 50%.

In the STOP-PD stabilization phase, 10% of participants who experienced remission with combination treatment had a relapse (Section 3.8). In contrast, Rothschild et al.⁴¹ found that none of the patients with PD who responded to combined fluoxetine and perphenazine had a relapse or dropped out during 12 weeks of *open-label* continuation treatment. Based on these data, we estimate that approximately 10% of acute phase full/near-remitters will not complete the 8-week open-label stabilization phase of the proposed study, either because of relapse or discontinuation. Thus, we predict that 176 participants will be available for the RCT.

3.9.3 Justification for Aspects of the Design:

Duration of Acute Treatment: Although most studies of the acute treatment of PD have been of 6-8 weeks duration,⁸ a maximum of 12 weeks of acute treatment is more suitable for this study for several reasons. First, one of the goals of the acute phase is to maximize the chance of achieving remission of delusions and antidepressant response, in order for participants to enter the RCT. In STOP-PD, 1/3 of participants who experienced remission with combined sertraline and olanzapine did not do so until between weeks 6 and 12 of treatment. Second, studies of 6-8 weeks typically use one cross-sectional assessment of $\geq 50\%$ decrease in severity of depression as the primary outcome criterion. The acute treatment outcome criterion that will be used in this study requires a longer period of observation. On the other hand, the decision to limit acute

treatment to a maximum of 12 weeks is based on study time frame considerations (completion of the study in 5 years) and the fact that patients who do not experience remission of psychosis and at least substantial improvement in depression following 12 weeks of intensive antidepressant-antipsychotic treatment should probably be considered for additional or alternative treatment.

Duration of Stabilization Phase: There are no data, and there is no consensus among experts,¹⁰² about how long to continue antipsychotic medication, once an episode of PD has responded to combination pharmacotherapy. However, a survey of 50 experts in the treatment of late-life depression found that the majority would not recommend stopping antipsychotic medication immediately after remission of PD.¹⁰² In the absence of data to the contrary, we believe that it is prudent to allow for a period of stability of remission of psychosis prior to withdrawal of the antipsychotic. On the other hand, continuation of the antipsychotic for too long exposes a patient to the hazards of ongoing weight gain and metabolic dysfunction. We therefore chose 8 weeks for the stabilization period to strike a balance between assuring *sustained* remission of the psychosis, while minimizing the duration of exposure to weight gain and metabolic disturbance.

Discontinuation Design: The primary aim of this study is to assess whether olanzapine, in combination with antidepressant medication, prevents relapse of PD. This question can be addressed through a double-blind RCT, in which placebo is substituted for olanzapine in half the study participants, at a fixed point in time. We also considered a placebo-controlled sequential discontinuation design, whereby placebo is substituted for olanzapine at different time points. Although a sequential discontinuation design could provide information about *how long* to continue olanzapine once an episode of PD has remitted, we believe that the first step is to determine whether or not antipsychotic medication is of any benefit in preventing relapse of PD. If antipsychotic medication is found to be beneficial, the next step would then be to assess the optimal duration of antipsychotic treatment. A sequential discontinuation design would require many more study participants than the design that we propose, and would therefore be more challenging in terms of recruitment and more costly than the current proposal.

Duration of the RCT: Limited data from naturalistic studies of PD suggest that when antipsychotic medication is discontinued, the 3 months after discontinuation is the period of greatest risk of relapse.^{32,41} The choice of 36 weeks for the proposed RCT therefore: a) covers the period of greatest risk of relapse of PD following the discontinuation of the antipsychotic, yet allows for a period of observation beyond that time, b) saves on the cost that would be associated with a longer study, and c) allows the study to be completed within 5 years.

Duration of Antipsychotic Taper: In the aforementioned open-label study of the withdrawal of antipsychotic medication in PD, Rothschild et al.⁴¹ tapered antipsychotic medication over a period of 4 weeks. No patient experienced discontinuation side effects or re-emergence of psychosis during the 4-week taper.

Stratification by Age: PD is prevalent in older adults with major depression.^{16,17,103,104} Age-related pharmacodynamic and pharmacokinetic changes may result in age-related differences in treatment efficacy and tolerability. It is therefore important to include a sufficient number of older persons in order to examine the relation between age, efficacy, tolerability, and safety.

Remission Criteria to Enter the RCT: Studies of major depression have found that partial improvement in depressive symptoms may increase the risk of subsequent relapse of depression.¹⁰⁵ We therefore believe that, in addition to experiencing full remission of psychosis, participants should experience substantial improvement in depressive symptoms prior to changes being made to the treatment to which they responded. There were patients in STOP-PD who experienced remission of psychosis and were rated by a research psychiatrist as 'very much improved' or 'much improved' on the CGI, yet had a final visit HAM-D score in the range of 11-15, which still represented $\geq 50\%$ improvement in the baseline HAM-D score. Given that patients in this study will continue with an antidepressant throughout the RCT, and may therefore continue to experience improvement in depression beyond the acute/stabilization phases of treatment, we will include persons with substantial improvement in depressive symptoms, even though the symptoms may not have reached the conventional $< 8-10$ HAM-D cut point for remission used in studies of non-psychotic depression.^{29,30}

MMSE Score ≥ 24 to Enter the Stabilization Phase: Persons with clinically significant cognitive impairment prior to the index episode of PD will be excluded from the study (Section 4.2.1). In addition, participants with a MMSE score < 24 at the end of the stabilization phase will be excluded from participation in the RCT (since poor cognitive performance at that stage of the study can not be explained by depression or psychosis), unless a MMSE score of < 24 is explained by factors other than cognitive impairment, such as low education level, visual impairment, or lack of fluency in the English language. Of the STOP-PD participants who achieved remission with combination treatment and participated in the stabilization phase, only 1/37 had a MMSE score

<24 at the end of stabilization. Thus, we expect that this exclusion will have minimal impact on subject flow in to the RCT.

3.9.4 Inclusion and Exclusion Criteria for participants are described in Human Subjects (Section 4.2.1)

3.9.5 Assessments and Measures:

Primary Clinical Measures pertain to the study’s aims and hypotheses and/or eligibility criteria. They are: Structured Clinical Interview for DSM-IV-TR (SCID-IV),¹⁰⁶ the GRID version of the 17-item HAM-D,^{98,107} Delusion Assessment Scale (DAS),⁹⁶ delusion and hallucination items of the SADS,¹⁰¹ Scale for Suicidal Ideation (SSI)¹⁰⁸, CGI,⁹⁹ and MMSE.¹⁰⁰ The 26-item Informant Questionnaire for Cognitive Decline (IQCODE)^{109,110} will be used to screen out clinically significant cognitive decline that began prior to the index episode of PD, to help avoid the inclusion of persons in the early stage of dementia.

Secondary Clinical Measures: Anxiety symptoms, medical burden, executive dysfunction, psychomotor change, and ‘treatment resistance’ during the index episode of depression have each been associated with increased risk of relapse/recurrence of major depression.¹¹¹⁻¹¹⁵ These variables will therefore be included as **covariates** in the Cox model examining risk of relapse (Section 3.10.3). The pertinent measures are: anxiety subscale of the Hospital Anxiety and Depression Scale,^{116,117} Cumulative Illness Rating Scale,¹¹⁸ DKEFS Stroop Conditions 1-3,¹¹⁹ the CORE⁹⁷, and the Antidepressant Treatment History Form.¹²⁰

• Given the age range of study participants, there will be 3 additional cognitive tests to help **characterize the sample at entry in to the RCT**; these tests, which target previously described impairments in PD¹²¹ and late-life depression,^{121,123} will be: i) a test of delayed recall (RBANS Immediate and Delayed Recall,¹²⁴ ii) a test of psychomotor speed (RBANS coding task¹²⁴), and iii) a test of cognitive flexibility (DKEFS Trail Making Test Conditions 4 & 5.¹¹⁹ The DKEFS and RBANS tests were selected as they have norms available for the entire age range of our proposed sample and the two DKEFS tasks and the two RBANS tasks were co-normed.

• Measures of non-metabolic safety will be: UKU Side Effects Scale;¹²⁵ Simpson Angus Scale;¹²⁶ Barnes Akathisia Scale;¹²⁷ Abnormal Involuntary Movement Scale;¹²⁸ Orthostatic hypotension assessed after standing for 1 minute, following 5 minutes in a supine position; and Falls Log (incidence and number of falls).

Anthropometric Measures : The selection of anthropometric measures and metabolic parameters is based on Consensus Recommendations regarding the clinical monitoring of patients treated with atypical antipsychotics.¹²⁹ Subjects will be weighed, and their height measured, in light clothing without shoes. In addition, pre-morbid weight (average weight in the year prior to the onset of the index episode of depression) will be obtained from the patient’s primary care physician’s records. When pre-morbid weight is not available from primary care physicians, the patient will be asked for this information. Pre-morbid weight will be used to calculate weight loss during the index episode of depression; depression-related weight loss will be taken in to account in a secondary statistical analysis of weight change during the proposed study. In addition to weight, body mass index (BMI) and waist circumference are key clinical measures of body fat.¹²⁹ BMI, a measure of weight relative to height, is an index of total body fat. Waist circumference, measured at the umbilicus, is a measure of abdominal obesity, which is more specifically associated with cardiovascular risk and metabolic syndrome than BMI.¹³⁰ BMI and waist circumference will be assessed at each study visit. Separate secondary statistical analyses pertaining to Aims 2-5 will be conducted, using each of these measures as an alternative to weight.

Metabolic Measures: Homeostatic model assessment (HOMA), a measure of insulin resistance^{131,132} and the primary measure of glycemic function in this study, will be calculated based on an established formula,¹³² each time fasting glucose and insulin are measured. HbA1c will be a secondary measure of glycemic function, to assess the longitudinal stability of serum glucose levels during the course of the study. Triglycerides and cholesterol (total, LDL, HDL) will also be measured.

Table 1: Schedule of Events: Acute and Stabilization Phases and RCT

Instrument	Baseline	Acute Phase ^{A, B} (week) (4-12 wks in duration)			Stabilization Phase ^C (week)		Discontinuation RCT ^C (week)															
		4	8	12 ^D	4	8	1	2	3	4	5	6	7	8	12	16	20	24	28	32	36 ^E	
SCID	x																					x
Clinical Ratings ^F	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight & Waist Circumference	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height	x																					

Metabolic Labs	x	x		x		x								x		x		x		x	x	
Drug Plasma Levels		x		x		x										x					x	
Genetic Testing	x																					
Biomarkers	x					x															x	
Baseline Physical ^A	x																					
Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Anxiety	x					x																
Medical Burden	x					x																
Cognition ^F	x					x															x	
Psychomotor Change	x					x																
ATHF	x																					
SF-36 ^I	x					x															x	
EPSE Ratings	x	x	x	x	x	x				x					x	x	x	x	x	x	x	
Best Guess Form ^J																					x	
Intent-to-Attend Form ^K						x																
Pill Count		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

^A The duration of the Acute Phase is variable and can last between 4 and 12 weeks, depending on time to response.

^B In-person clinical evaluation will be performed by a research psychiatrist at weeks 1,2,3,6, and 10 of the Acute Phase (more frequently for inpatients) in order to provide intensive clinical monitoring during the early part of the study.

^C Participants will have over-the-phone clinical evaluation by research associates (RAs) at weeks 2 and 6 of the Stabilization Phase and weeks 10, 14, 18, 22, 26, 30 and 34 of the RCT, so as to allow for close clinical monitoring throughout these phases of the study, yet lessening the burden on participants that would be associated with more frequent in-person assessments. During the phone assessments, RAs will administer the SCID major depressive episode questions, the SSI, and the DAS conviction items. These clinical assessments will be reviewed by a research psychiatrist. Participants with evidence of clinical deterioration will be promptly seen in person by a research psychiatrist and RA.

^D These assessments will be completed at the end of the Acute Phase, which occurs between 4 and 12 weeks after starting study medications.

^E These assessments will be completed at week 36 or at the point of termination.

^F Primary clinical ratings are HAM-D, DAS, SADS delusion and hallucination items, SSI, and CGI. In addition, the UKU side effects scale, Falls Log, and Concomitant Medication Log will be completed at these visits.

^G Baseline physical includes physical examination and screening lab tests (CBC; serum electrolytes, creatinine; liver function tests (AST, ALT); TSH; Vitamin B12; serum pregnancy test; urine drug screen) and EKG if they have not been done in the week prior to starting the study.

^H Cognitive evaluation will include: the IQCODE at baseline; and the MMSE, Immediate and Delayed Recall, Stroop, Trail Making, and Coding task at the end of the Stabilization Phase, and Delayed Recall, Stroop, Trail Making, and Coding task at RCT termination.

^I The SF-36 will be administered to: i) examine the association of acute and remitted psychotic depression with participants' health-related quality of life, and ii) explore the effect of continuation versus discontinuation of antipsychotic medication on participants' health-related quality of life.

^J The Best Guess Form will be completed independently by participant and rater at RCT termination, to determine, once the study is completed, whether participants and/or raters could guess treatment assignment on a greater than chance basis. This will serve as an indicator of how well the study's double-blind was preserved.

^K The purpose of the Intent-to-Attend form is described in Section 3.10.5 ('Strategies for Attrition')

Rater Training and Rater Reliability: All raters will participate in standardized training before being allowed to assess and rate study participants. In addition, inter-rater reliability of the HAM-D and DAS will be assessed on an annual basis. Please see 'Reliability and Quality Control' in Section 4.1.6 for full details.

3.9.6 Pharmacogenetics: Processing of DNA: Whole blood on all consenting participants will be sent directly to the NIMH Center for Collaborative Genetic Studies ('the Center') for the generation of cell lines and extraction of DNA. Blood samples will be sent as they are collected and shipped at room temperature using the Center's established protocols that are designed to minimize trauma. In the rare event that a sample is lost in transit, or if the sample is unsuitable for DNA extraction, or if a cell line is not successfully made, we will obtain a repeat blood sample to send to the Center. DNA will be shipped from the Center to Dr. James Kennedy's genetics laboratory at CAMH in Toronto within 4 months of the blood sample being received by the Center. With the exception of data entry personnel at Cornell, the study's research staff will not be privy to the genetic data until after the study has finished, so as to maintain the blind.

Genotyping: We will use standard TaqMan methods on our ABI-7500 for SNP markers and ABI-3100 for repeat polymorphisms. To ensure a clear result, any ambiguous genotypes will be discarded and the participant's DNA will be re-genotyped until the results are unambiguous. 10% of the participants will be re-genotyped to check for error rates (the test error rate in Dr. Kennedy's lab is 0.5%). We will type selected SNPs (functional and certain tagged SNPs) across the candidate genes described in Section 3.6, and also explore any highly promising genes emerging from the literature. We will test both single markers and haplotypes.

Population Stratification will be examined using the STRUCTURE program.¹³³ We will select a set of unlinked SNPs from our set of selected markers, augmented by an additional 96 markers that are known to be ‘ancestry informative’ and run the STRUCTURE program under an admixture model, assuming correlated frequencies, with 20,000 burn-ins and 20,000 repetitions. The group membership probabilities thus obtained would be used as a covariate in the pharmacogenetic statistical analyses.

3.9.7 Drug Exposure: Pharmacokinetic changes associated with aging and other factors^{134,135} can result in variability of drug concentrations, which in turn can result in differences in pharmacodynamics. Drug exposure is therefore an important piece of information when interpreting variability in treatment efficacy and adverse effects.^{134,136} Blood will be collected for determination of plasma sertraline and olanzapine concentrations. Each site will send frozen batched plasma samples to Dr. Pollock’s psychopharmacology lab in Toronto every 6 months for pharmacokinetic analyses. The analytic strategy will use population pharmacokinetics which uses nonlinear mixed effect modeling¹³⁷ to identify intra- and inter-individual sources of variability. The modeling provides: (1) magnitude of exposure, expressed as average drug concentration or Area Under the Curve, and (2) variability of exposure from what is expected, expressed as a ratio of the predicted drug concentration for a given time point to the observed concentration (Cpred/obs). Variability from the norm in drug concentrations can be determined using sparse (between two and four) plasma samples per patient.¹³⁸

3.9.8 Outcomes

Outcome Criteria: Relapse is the primary measure of outcome. Relapse criteria are broad, to reflect a range of clinically relevant outcomes of PD. The criterion for relapse will be at least one of the following: 1) SCID symptoms of major depressive episode (preferably maintained for at least 1 week over two consecutive weekly visits); 2) 17-item HAM-D score of ≥ 18 (preferably maintained for at least 1 week over two consecutive weekly visits) and a mean absolute increase of 5 points on at least one visit relative to entry into the RCT; 3) re-emergence of SCID-rated psychosis (delusions or hallucinations) (preferably for at least 1 week over two consecutive weekly visits) and a score of ≥ 3 on the SADS delusion or hallucination severity items (delusion/hallucination ‘definitely present’); 4) significant clinical worsening, defined as either i) emergence of ‘high risk’ of suicide at any time (current suicide plan or suicide attempt), and/or ii) development of SCID-rated mania or hypomania (preferably for at least 1 week over two consecutive weekly visits), and/or iii) psychiatric hospitalization for depression, psychosis, suicidality, or mania/hypomania, regardless of the duration of these symptoms. Although a one-week time duration is preferable, the research psychiatrist is allowed to declare that a relapse has occurred if the clinical criterion is established at an in-person visit and postponing further intervention for another seven days is considered to place the subject at undue risk. Time to relapse will be defined as time from randomization to the first visit at which relapse is established or the start of psychiatric hospitalization. These relapse criteria reflect a clinical deterioration for which most clinicians would consider a change of treatment. Even though patients with a history of bipolar affective disorder will not be allowed to enter the study (Section 4.2.1), mania or hypomania is included as an outcome variable because onset of PD in younger adults may predict subsequent development of bipolar affective disorder. Participants who are suspected of having a relapse will be seen by one of the study’s research psychiatrists who will determine whether relapse criteria are met.

Management of Relapse: Patients who meet relapse criteria will be seen for clinical management by a psychiatrist at the research site who is not affiliated with the study within 48-72 hours of referral. Alternatively, patients can be referred for acute psychiatric hospitalization, if deemed appropriate by the study psychiatrist. The non-study psychiatrist will be notified by the research pharmacist whether the patient was taking olanzapine at the time of relapse. Other research personnel will not be aware of the treatment assignment. Based on the frequency of relapse postulated for the study, we estimate that there will be an average of 3 cases of relapse per year per study site.

3.9.9 Pharmacotherapy: Please see the appended Pharmacotherapy Protocol (Appendix1) for full details regarding pharmacotherapy in all phases of the study.

Acute phase: The only psychotropic medications allowed in the study will be i)olanzapine, ii)sertraline, and iii)‘as needed’ lorazepam and benztropine (doses of lorazepam and benztropine will not be permitted in the 12 hours prior to psychometric testing, so as to minimize the effect of these medications on cognitive performance). Psychotropic medications that are not permitted in the study will be withdrawn prior to starting study medications, but if this is not feasible, by the end of the first week of the study. Sertraline and olanzapine will be dispensed in a non-blind, open-label fashion during the acute and stabilization phases of the study. The titration schedule of sertraline and olanzapine, and the target dosages of these medications, will be the same as that successfully employed in STOP-PD. Sertraline will be started at 50mg/day and increased by 50 mg

increments to reach a target dose of 150 mg/day by the end of the first week of treatment. Participants who did not experience at least partial improvement (based on operationalized criteria) in depressive symptoms, after taking sertraline at a dosage of 150 mg/day for 4 weeks, will have the sertraline dose increased to 200 mg/day, as tolerated. Olanzapine will be started at 5 mg/day and increased by 5 mg increments to reach a target dose of 15 mg/day by the end of the first week of treatment. If there is no improvement or inadequate improvement in psychosis after 7 days of 15 mg/day of olanzapine, the dosage of olanzapine will be increased to 20 mg/day, as tolerated. Slower titration or temporary dose reductions of one or both medications will be allowed if there are clinically significant side effects, but a concerted effort will be made to achieve the target dosages, as tolerated.

Stabilization Phase: When participants meet remission criteria, they will continue with open-label sertraline and olanzapine during the 8-week stabilization phase. Since the goal of this phase is to consolidate stability of remission, adjustment of the doses of study medications will be allowed, if necessitated by clinical worsening or significant side effects. The maximum allowable daily dosages of sertraline and olanzapine, respectively, will be 200mg and 20mg, and the minimum allowable daily dosages will be 50mg and 5mg. Because *sustained* remission of psychosis during the stabilization phase will be required for eligibility for the RCT, participants will leave the stabilization phase if they experience a relapse of delusions or hallucinations during that time as determined by SCID interview.

Randomized Phase: Participants who meet the study's remission criteria will be randomly allocated, following completion of the stabilization phase, to either continue olanzapine or switch, over a period of 4-weeks, from olanzapine to placebo. All participants will take open-label sertraline for the duration of the RCT. The goal will be to maintain sertraline at the same acute dose that the participant was prescribed at the time of randomization to the RCT. Because participants will have taken sertraline for a minimum of 10 weeks before entering the RCT, we anticipate that the dose of sertraline will rarely need to be adjusted in the RCT because of side effects. However, a reduction of the dosage of sertraline will be allowed if the site PI agrees. An increase in dose of sertraline will not be permitted at any time during the RCT, because it will confound testing of H1. The goal will be to maintain olanzapine/placebo at the same acute dose that the participant was prescribed at the time of randomization to the RCT. However, a change in dose of olanzapine/placebo will be permitted, if necessitated by adverse effects or clinical worsening during the RCT, following discussion with the site PI. The rationale for allowing a change in olanzapine/placebo dose, is that the primary aim of the study is to assess whether olanzapine, administered within a clinically relevant dose range, prevents relapse, not whether a specific dose of olanzapine prevents relapse. Dose changes of sertraline and olanzapine/placebo will be carefully recorded and will be reported in a descriptive fashion for each treatment arm.

3.10 DATA ANALYSIS

3.10.1 Data Management is described as a part of Quality Control in Section 4.1.6.

3.10.2 Randomization: We will randomize 88 participants to each of the two treatment arms using a 1:1 allocation ratio, stratified by age, remission group at randomization, and site. In order to reduce the probability that a disproportionate number of subjects are randomized to any one level of the factors a blocking strategy will be used. Randomization will be conducted by Dr. Leon, the study's statistician, using the Dallal software.

3.10.3 Data Analytic Procedures: Initially, baseline demographic and clinical characteristics will be examined. Frequency distributions will be produced. Descriptive and graphical displays will be produced. Transformations will be used when distributional assumptions are not fulfilled for inferential tests. Treatment groups will be compared on baseline demographic and clinical variables using t-tests for continuous variables, Mann-Whitney tests for ordinal variables, and chi-square tests for categorical variables. If significant baseline group imbalance is detected on any particular variable, that variable will be included as a covariate in the inferential analyses if its correlation with outcome is 0.30 or greater. Dropouts and completers will also be compared on baseline variables using t-tests, Mann-Whitney tests, or chi-square tests. The primary analyses will adhere to the Intent-to-Treat principle. Each statistical test for H1-3 will involve a two-tailed alpha of .05.

Primary Hypothesis: Efficacy.

H1: The combination of sertraline and olanzapine will be associated with less risk of relapse than the combination of sertraline and placebo. H1 will be tested with a Cox proportional hazards model that compares survival time across treatment groups. Survival time will be defined as time from randomization to relapse (Section 3.9.8) and will be measured in weeks. A subject's survival time will be classified as censored at the point of study discontinuation, (e.g., due to withdrawal of consent or a severe intervening non-psychiatric medical event) or at end of follow-up, if relapse has not yet occurred. Kaplan Meier survival curves will be used

for descriptive analyses of time to relapse. The Cox models will include treatment group and the stratification variables: site, remission group at randomization (full-remission vs. near-remission), and age group at randomization (18-59 vs. ≥ 60 years). Treatment groups will be compared on 5 variables at the time of randomization that have the potential to be associated with risk of relapse (anxiety, medical burden, executive dysfunction, psychomotor change, and treatment resistance prior to study entry; Section 3.9.5); if the treatment groups differ significantly on one or more of these variables ($p \leq .05$) and the variable in question is correlated with relapse ($r > .30$), the variable will be included as a covariate in the Cox model. Based on our prior studies,^{38,41,139} we expect no more than 10% attrition during the RCT among these participants who have already been enrolled for 12-20 weeks prior to randomization and who are in sustained remission at the time of randomization. This attrition rate might appear to be low, but this is because those subjects most vulnerable to attrition will likely drop out in the phases prior to randomization. Non-informative censoring will be examined by comparing those who do and do not dropout on their HAM-D ratings from the prior week. The constant hazards assumption will be examined by examining the incremental contribution of a treatment x vulnerable period of relapse interaction (exploring the possibility of higher risk in the first 3 months following discontinuation).

Secondary Hypotheses: Weight and Metabolic Safety

H2: The combination of sertraline and olanzapine will be associated with higher weight, higher total cholesterol, and higher triglycerides compared with the combination of sertraline and placebo in the randomized phase. This will be tested using separate mixed-effects linear regression analyses for weight, cholesterol, and triglycerides during the randomized phase. Models will include up to 15 repeated assessments of weight and up to 5 repeated measures of total cholesterol and triglycerides over the 36-week trial, as the respective dependent variables. Using a regulatory approach to safety analyses (H2, H3, E1 and E2), we will classify subjects based on medications taken during protocolized treatment. Likelihood ratio (LR) tests will successively examine the incremental contributions of a quadratic term for time and two interactions (treatment by site and treatment by time).¹⁴⁰ The decision rule calls for rejection of H_0 if the latter interaction is statistically significant. Interaction and quadratic terms will only be included in subsequent models if statistically significant. LR tests will determine if the time better approximated with weekly time indicators that allow for other forms of non-linear change over time. In addition a spline-based approach will examine metabolic changes. If a participant receives new treatment or a change of treatment for hyperlipidemia during the RCT, his/her pertinent metabolic data from that point onwards will be excluded from the mixed model, although the metabolic measures in question will continue to be collected for safety analyses and reporting to the DSMB. Based on data from STOP-PD, we expect that fewer than 5% of participants (i.e. <10 participants in the RCT) will have metabolic data censored for this reason. We chose not to include these post-randomization metabolic data as covariates in the mixed model, because doing so could confound 'cause and effect' and result in a biased estimate of the treatment effect, thereby compromising the primary goal of the analysis.¹⁴¹

H3: Older age will be associated with less weight gain during the open-label phase. Mixed-effects linear regression analysis will examine weight change from Acute Phase baseline. The model will include up to 6 weight assessments over the 12-20 week acute and stabilization phases. We will use the strategy above (H2) except that age will be the primary fixed effect because treatment is a constant in the open-label phase. LR tests will examine incremental contributions of a quadratic term for time and the age by time interaction. In addition a spline-based approach will be used to fit metabolic measures. H_0 will be rejected if the interaction is statistically significant.

Exploratory Analyses

E1. Explore older age as a moderator of change in weight and metabolic variables during the randomized phase. Analyses of age as a moderator are exploratory and, as recommended¹⁴² will focus on the magnitude of the effect and not involve significance testing. Separate mixed-effects linear regression models will examine change on weight, total cholesterol, triglycerides, and insulin resistance.

E2. Explore the association of selected genetic polymorphisms with: i) remission, ii) relapse, and iii) weight and metabolic variables during the open-label and randomized phases of the study. We will apply quality control for the genotyped genetic markers: i) all tag SNPs with a call rate less than 95% and minor allele frequency less than 10% will be excluded to provide sufficiently informative variation, and ii) we will test for Hardy-Weinberg equilibrium (HWE) for each marker; markers not in HWE will be discarded ($p < .001$). The analyses for remission and relapse will compare those with and without each candidate genotype on time until remission/relapse in separate Cox proportional hazards models. Analyses will examine one genotype per model. Mixed-effects linear regression analyses will compare those with and without each candidate genotype on weight and metabolic variables. There will be separate models for weight and each pertinent metabolic

variable; these analyses will examine one genotype per model. Each open-label analysis will involve a main effect of genotype, whereas each randomized phase analysis will involve both the main effects and interaction of genotype and randomized treatment. Haplotype analyses will follow the same approach as for genotype analyses. Haplotypes occurring at a frequency of <10% will not be included in analyses.

Analysis of Non-Metabolic Safety Data: Data on non-metabolic adverse events during each phase will be collected for reporting to the DSMB. In addition, these data during the RCT will allow for a descriptive comparison between participants maintained on olanzapine and those switched to placebo. For each phase of the study, we will report the number and % of participants who meet criteria for specific adverse events, who did not meet these criteria at acute phase baseline. Adverse events will be defined as: an increase of ≥ 2 points from baseline or a score of 3 on individual items of the UKU; a global severity score of ≥ 2 on the AIMS; a global assessment score of ≥ 2 on the Barnes Akathisia scale; a mean score of ≥ 2 on the Simpson Angus Scale; a score of ≥ 1 on item #4 or #5 of the SSI; a reduction in systolic blood pressure of ≥ 20 mm Hg or in diastolic blood pressure of ≥ 10 mm Hg within 3 minutes of standing; one or more falls. We will also report the N and % of individuals who meet criteria for an adverse event from week 8 onwards of the RCT, to allow for the possibility of improvement in adverse effects once open-label phase olanzapine is cleared from the body. We will also report the N and % of individuals who are started on a lipid-lowering or glucose-lowering drug after study enrollment. Because of the large number of variables, these data will be presented descriptively.

Analysis of Drug Exposure: The analyses of drug exposure are exploratory and will not directly influence the findings of H1-3 and E1-2, but will instead provide supplementary information for interpretation of these findings. Mixed effects linear regression analyses will compare treatment groups on magnitude and variability of sertraline exposure in the randomized phase. Mixed effects linear models will compare age groups on magnitude and variability of i) sertraline exposure and ii) olanzapine exposure during the open-label and randomized phases. There will be separate models for each phase and for each measure of drug exposure.

3.10.4 Sample Size Determination and Statistical Power Analyses:

Assumptions for Power Calculations for H1: We propose 20% as the minimal clinically meaningful difference in relapse rates between olanzapine and placebo over 36 weeks. A 20% difference would mean that 5 patients (NNT) would need to be treated with olanzapine to prevent 1 case of relapse. Based on the review of literature (Section 3.4) and STOP-PD stabilization data (Section 3.8), we estimate that 15% of participants who are maintained on sertraline+olanzapine will have a relapse in the RCT. A relapse rate of 35% in the sertraline+placebo group would therefore be consistent with the hypothesized 20% difference between treatment groups. A 35% relapse following olanzapine discontinuation is the same as the rate reported by Aronson et al.³² in a naturalistic study of antipsychotic discontinuation in PD, but not as high as some of the rates of relapse of PD following cessation of a course of ECT.^{4,37-39} Based on our previous experience of conducting studies of the continuation and maintenance treatment of PD,^{38,41,139} we predict that attrition during the RCT will not exceed 10%.

Table 2. Statistical Power for Survival Analyses for H1.

Sert + Pla Relapse	Sert +Olanz Relapse	Attrition	Power
40%	15%	10%	0.95
40%	15%	15%	0.94
35%	15%	10%	0.84
35%	15%	15%	0.82
35%	10%	10%	0.98
35%	10%	15%	0.97

Power calculations for H1: The sample size proposed for this study was determined based on statistical power analyses for the primary hypothesis (H1), which will be tested with survival analysis. The protocol specifies randomization of a total of 176 participants (88/group), and specifies a two-tailed alpha level of .05. Power was estimated in a simulation study using S+ survfit. The proposed sample size will provide sufficient statistical power to detect clinically meaningful differences in H1 (Table 2).

Assumptions for Power Calculations for H2: 1) Data from RCTs in schizophrenia show that olanzapine-related weight gain slows after the first 12 weeks of treatment¹⁴³ but can continue by an average of 1lb/month for up to 9 months of treatment.¹⁴⁴⁻¹⁴⁶ In the post-acute stabilization phase of STOP-PD, weight gain slowed to an average 1.5lbs/month; 2) We propose that participants assigned to placebo will lose most, but not all, of the weight gained during the open-label phase of the study, because some of the weight gained will have been restoration of depression-related weight loss; 3) Ongoing increases in triglycerides, averaging 8-10 mg/dl/month over periods of 4-12 months, have been reported with olanzapine in studies of schizophrenia.¹⁴⁵⁻¹⁴⁷ In STOP-PD, there was a similar mean increase of approximately 9mg/dl/month. We therefore assume an increase in triglycerides in the olanzapine arm of the RCT; 4) RCTs of schizophrenia report only a slight increase in total cholesterol with olanzapine after the first 12-16 weeks of treatment.^{145,146} We therefore

assume little or no change in total cholesterol from randomization values in the olanzapine arm; 5) We hypothesize that triglycerides and total cholesterol in placebo-treated patients will return towards acute phase baseline values.

Table 3: Statistical Power of Mixed-Effects Linear Regression Analyses for H2 and H3

# observations /subject	Standardized Effect	ICC=.50 Lipids	ICC=.95 Weight
4	.35	.74	.77
4	.40	.84	.85
4	.45	.89	.93
8	.35	-	.80
8	.40	-	.89
8	.45	-	.95

Power Calculations for H2 (Weight and Metabolic During RCT) : Power was estimated in a simulation study using SAS PROC MIXED. To account for attrition in H2, the power analyses assumed we would collect at least 8 of 15 repeated assessments of weight and 4 of 5 measures of total cholesterol and triglycerides during the RCT. The proposed design will have power $\geq .80$ to detect differential slopes that result in standardized differences at

endpoint $\geq .35$ for weight and $\geq .40$ for triglycerides and total cholesterol. To put these in perspective, based on STOP-PD data, these effects correspond to group differences as small as 4.9 lbs in weight, 38 mg/dl in triglycerides, and 22 mg/dl in total cholesterol.

Assumptions and Statistical Power for H3 (Weight During Open-Label Phase): Power analyses for H3 assumed that we would collect at least 4 of the 6 planned assessments of weight during open-label treatment. The proposed design will have power $> .80$ to detect differential slopes that result in a standardized difference as small as .40 by the end of the open-label phase (Table 3). To put this in context, of the participants in STOP-PD who completed 12 weeks of acute treatment, the younger group gained a mean 16.6 ± 16.5 lbs and the older group gained a mean 10.7 ± 11.3 lbs; the standardized effect size for this weight difference was 0.42.

3.10.5 Strategies for Attrition: Attrition can introduce bias and reduce power, precision and generalizability.¹⁴⁸ Based on our prior studies, we expect no more than 10% attrition during the RCT (see above). Cox models assume non-informative censoring. The assessment frequency allows us to gauge survival status no more than 2 weeks prior to dropout. Also, for the survival analysis of H1, we will adhere to the Intent-to-Treat principle, in that we will make every effort to continue assessments for the entire course of randomized treatment or until relapse (which ever comes first), even among those nonadherent to randomized assignment.^{149,150} Mixed models (H2, H3, E1, E2) yield valid inferences assuming ignorable attrition (i.e. attrition is accounted for by covariates/dependent variable measured prior to drop-out).¹⁵¹ Following the regulatory approach to safety, we will classify subjects based on medications taken during protocolized treatment. We will examine the ignorable attrition assumption. First, using a pattern mixture model,¹⁵² implemented in a longitudinal framework.¹⁵³ Second, Intent-to-Attend at entry to the RCT will be used as a covariate to account for attrition.¹⁵⁴ Estimates of treatment effect from the models described above will be compared with models that also include the main effects of either dropout pattern or Intent-to-Attend.

4. PROTECTION OF HUMAN SUBJECTS

4.1. LEADERSHIP PLAN TO PROTECT THE INTEGRITY OF HUMAN SUBJECT DATA COLLECTED ACROSS MULTIPLE SITES

4.1.1 Rationale: This grant proposal is a Renewal (formally known as Competing Continuation) of a NIH-funded U01 'Acute Pharmacotherapy of Unipolar Psychotic Depression' (MH62446, MH62518, MH62565, and MH62624). This U01 is also known as the Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) for the purpose of communications, presentations of research findings, and publications. The change in title of the renewal, 'Sustaining Remission of Psychotic Depression' reflects the focus of the proposed study on treatment of PD beyond the acute phase.

STOP-PD was a multi-center study involving the following four sites: Weill Medical College of Cornell University (PI: Dr. Barnett Meyers), University of Toronto (PI: Dr. Alastair Flint), University of Massachusetts Medical School (PI: Dr. Anthony Rothschild), and University of Pittsburgh School of Medicine (PI: Dr. Benoit Mulsant). The coordinating centre for STOP-PD was based at Cornell, under the leadership of Dr. Meyers, who was the overall principal of the study. The STOP-PD grant proposal was submitted as four identical R01s. At the time of funding, the mechanism was changed to U01s by NIMH, consistent with the approach taken by NIH with other multi-center clinical trials.

The proposed study will include the same sites as STOP-PD. At Cornell University, University of Massachusetts, and University of Toronto, the same principal investigators as in STOP-PD will serve as principal investigators of the new study. At the Pittsburgh site, Ellen Whyte M.D. will serve as principal investigator for that site. Dr. Whyte joined the STOP-PD PI team in September 2005, when Dr. Mulsant partially relocated to the University of Toronto. She assumed day-to-day operations of the Pittsburgh site and actively participated in the overall leadership of the previous study through participation in the study's Steering Committee and Publications Sub-Committee, participation in weekly conference calls and annual face-to-face meetings with the principal investigators from the other sites, reviewing and approving the results of data analyses, presenting findings at scientific meetings, and writing and publishing manuscripts. In the proposed study, Dr. Mulsant will serve as a co-investigator at the Pittsburgh site (in addition to his leadership role at the Centre for Addiction and Mental Health [CAMH] consortium site in Toronto), and will continue to collaborate closely with Dr. Whyte in the management of this site.

Use of multiple sites (through the Collaborative Clinical Studies of Mental Disorders mechanism [PAR-09-153]) is justified by the fact that the majority of patients with PD need to be recruited from inpatient settings due to the severity of their illness. Recruiting and retaining patients in a treatment study of PD is labor intensive and challenging; a single site would not be able to recruit and retain the number of patients with PD that are needed for the proposed study.

4.1.2 Experience And Background: Drs. Meyers, Flint, Mulsant, and Rothschild have many years of experience in conducting research in PD. The principal investigators of the proposed study have worked as a group on STOP-PD for the past 8 years. This collaboration has involved: conceptualization, formulation, writing, and revision of the STOP-PD grant application; recruiting and training of research personnel; recruitment and treatment of participants in the study; data collection and oversight of the transfer of data to the coordinating center; membership of, and participation in, the study's Steering Committee and Publications Sub-Committee; participation in weekly conference calls and annual face-to-face meetings; reviewing and approving the results of data analyses, presenting findings at scientific meetings; and writing and publishing manuscripts. This partnership will continue in the proposed renewal. The successful completion of STOP-PD, including meeting the planned recruitment target, is testimony to the successful collaboration of this group of investigators.

In addition to leading STOP-PD, Dr. Meyers has other experience in leading and coordinating multi-center studies. Dr. Meyers used support from a R24 award (MH53816) to develop a clinical mental health services research infrastructure that completed 10 pilot projects at 16 diverse sites. These studies recruited 2,500 subjects, and managed systematically collected 6-month longitudinal data on 250 patients with major depression from multiple primary care and mental health sector sites.

4.1.3 Site Functions: Dr. Meyers will be the overall principal investigator of the proposed study, with support in this role from Dr. Flint. The coordinating center will be based at Cornell. The inter-site project coordinator, data manager, and the project's statistician/methodologist will be based at Cornell. Other investigators associated with the Geriatric Psychiatry Institute at Cornell (Drs. Alexopoulos, Bruce, and Young) have several R01s, R24 research infrastructure grants, as well as a U01, that allow for synergy in supporting and sharing research staff between projects at Cornell. In addition, the Institute's Advanced Centre for Interventions and Services Research (PI: Alexopoulos GS) will contribute to infrastructure support for research operations at Cornell, as it did for STOP-PD. Each study site will contribute equally to recruitment of patients. Pharmacogenetic and pharmacometric analyses of the proposed study will be conducted in Toronto, in the research laboratories of Drs. James Kennedy and Bruce Pollock, respectively.

Table 4: Functions Performed by Each of the Four Sites

Function	Site	Areas of Primary Responsibility
Subject recruitment & clinical management	All four sites	<ul style="list-style-type: none"> Each site will recruit 98 acutely ill participants and randomize 44 remitted participants, with anticipated differences in race and ethnicity as described in Section 7; Recruitment and subject management are identical across sites

Coordinating Center	Cornell	<ul style="list-style-type: none"> • Coordinates and oversees research activities across sites; • Inter-site Coordinator communicates with and monitors activities of site raters and reports to Principal Investigators; • Assures adherence to the Study Manual; • Assures completeness and quality of data; manages data base; • Chairs Steering Committee and Publication Committee; • Communicates with regulatory bodies and external agencies
Recruitment, Assessment, and Adherence	University of Toronto; Cornell	<ul style="list-style-type: none"> • Develops the Study Manual; • Coordinates training on clinical assessments and reliability testing in collaboration with the Cornell Inter-site Project Coordinator; • Provides leadership for monitoring recruitment, retention, and medication adherence; coordinates strategies to overcome obstacles
Neuropsychological Training	Pittsburgh	<ul style="list-style-type: none"> • Conducts training and annual re-training on neuropsychological assessments and coordinates analyses of test results
Methodology, Data Management and Data Analysis	Cornell	<ul style="list-style-type: none"> • Provides centralized data management for all sites; • Provides methodological leadership and consultation (e.g., blinding, consistency across sites, reliability assessments); • Provides biostatistical leadership for analyses of project data
Pharmacokinetics and Pharmacogenetics	Toronto	<ul style="list-style-type: none"> • Oversees quality assurance efforts regarding sample acquisition, pre-processing, and storage; • Carries out all pharmacokinetic and pharmacogenetic assays; • Applies population pharmacokinetic modeling to the drug concentration data

4.1.4 Roles and Responsibilities of PIs: The principal investigators will be responsible for hiring, training, and supervising research staff at their respective sites, overseeing the recruitment and retention of patients at their sites, overseeing the quality of data collection, and ensuring that data are sent to the Coordinating Center in a timely manner. In addition, each of the principal investigators will be members of the study's Steering Committee and Publications Sub-Committee.

In addition to these general responsibilities, the investigators will have specific functions. Dr. Meyers will lead the Coordinating Center, which will coordinate the research activities at the 4 sites. He will oversee the work of the project coordinator, who will be a Ph.D. clinical psychologist, and the data manager. He collaborate with Dr Andy Leon, who will serve as the study's statistician/methodologist. Along with Dr. Flint, he will co-chair the study's Steering Committee. He will chair weekly telephone conference calls attended by the PIs, the Coordinating Center's staff, and the NIH project officer, and prepare minutes summarizing the discussion and action items arising from each of these calls. Dr. Meyers and Coordinating Center staff under his supervision will prepare quarterly reports and if needed, interim reports, for the NIMH Data and Safety Monitoring Board, communicate with the NIMH project officer, and monitor the study's overall budget.

Dr. Flint will be responsible for overseeing development of the manual of study operations and case record forms, overseeing overall recruitment of participants across sites, and overseeing both rater training and assurance of inter-rater reliability across sites. These responsibilities will be carried out in collaboration with the inter-site project coordinator under the direction of Dr. Meyers. Drs. Flint and Meyers collaborated successfully in the implementation and operations of the recently completed STOP-PD. Dr. Flint will work with Gary Lewis M.D., the endocrinologist consultant at the University of Toronto, in coordinating the analyses of the metabolic data and interpreting these data.

Dr. Mulsant, who has appointments at both the University of Toronto and University of Pittsburgh, will oversee the genetic and pharmacometric aspects of the study. He will collaborate closely with Drs. Kennedy and Pollock, both based at CAMH in Toronto, with respect to all aspects of these analyses, and will take the lead in preparing reports pertaining to these data.

Dr. Whyte will collaborate with Meryl Butters, Ph.D., a neuropsychologist at the University of Pittsburgh, who will supervise the collection of all neuropsychological data. Dr. Butters will train and re-train site raters in the administration of neuropsychological tests.

4.1.5 Governance: The Steering Committee, composed of the 4 principal investigators and Dr. Mulsant, and co-chaired by Drs. Meyers and Flint, will be responsible for oversight of the research. The committee will have weekly telephone conference calls that will review progress at the 4 sites, including recruitment and retention of participants, adherence to study procedures, and the safety of participants. Protocol violations, serious adverse events, and obstacles to the study's progress will be discussed. Email will be used for as-needed communication between conference calls, unless an urgent operational issue dictates the scheduling of a special conference call. The Steering Committee will receive and review reports from the inter-site project coordinator about results of reliability testing and the status of reliability training exercises. The Steering Committee will also meet in person for a 1-day meeting, at a minimum frequency of once per year. A publications sub-committee will be composed of the principal investigators and Dr. Mulsant as standing members; co-investigators will be invited on an ad hoc basis, as appropriate. The publication sub-committee will plan for data analyses, presentation of results at scientific meetings, and manuscript preparation, in collaboration with the data manager and statistician, and will make decisions about authorship. All manuscripts using project data will be reviewed and approved by the Publications Sub-committee before submission. In the event of any disagreement pertaining to the study amongst the members of the Steering Committee, that is not resolved through discussion, a vote will be taken and the majority will prevail.

4.1.6 Reliability and Quality Control:

Rater Training and Rater Reliability. Research associates at each site will be trained by the site's study coordinator and primary investigator in the administration of the instruments. General oversight of this training will be provided by the Coordinating Center's Project Coordinator, in collaboration with Dr. Flint and Dr. Meyers. The project coordinator will have biweekly conference calls with Dr. Meyers and Dr. Flint to report on study progress. Training of research associates at each site will involve the following: the observation and discussion of training videotapes supplied by the Cornell Coordinating Center pertaining to the primary instruments (SCID, HAM-D, DAS, and SSI); in-person observation of interviews conducted by research psychiatrists and experienced research coordinators; and in-person supervision of training interviews conducted by research associates. A 2-day launch meeting will take place at the Cornell Coordinating Center prior to the start of the study, to solidify this training and to review rating conventions of each scale. Meryl Butters Ph.D. will attend the launch meeting to train the research team on the proper administration of the neuropsychological instruments. Research associates will receive ongoing supervision from research coordinators and research psychiatrists at each site. In addition, the inter-site Project Coordinator will lead weekly conference calls with the site study coordinators and research associates. These calls will address subject recruitment and retention, training and reliability of research personnel, the completeness and accuracy of data entry, and other quality assurance issues.

Inter-rater reliability of the HAM-D and DAS will be assessed on an annual basis. Reliability assessments will require research associates and research coordinators at each center to independently rate 12 videotaped interviews of patients with varying levels of severity of psychotic depression. Inter-rater reliability assessments performed during each year of STOP-PD yielded ICCs of 0.93-0.98 for the GRID HAM-D total score and 0.69-0.84 for the conviction dimension of the DAS, demonstrating good reliability for these primary measures. One-day working meetings in Years 2-4 will be attended by the principal investigators, research coordinators and associates, and inter-site Project Coordinator to address study operational issues, rater training, and inter-rater reliability.

Data Management and Data Integrity. The coordinating center at Cornell will be responsible for standardizing data collection forms and data entry procedures, ensuring the reliability and completeness of data entry, and overall data integrity across all 4 sites. The Coordinating Center will also be responsible for data analyses. Dr. Meyers will receive weekly reports from the project coordinator and the data manager on activities at participating sites, and review these reports with the Steering Committee.

During the start-up phase, the data manager and Dr. Leon will help standardize data collection forms and data auditing procedures across the four sites in collaboration with the Cornell Inter-Site Project Coordinator. The data management team has developed a set of standards and procedures for data entry and checking and for the documentation of data sets generated for statistical analysis. These methods, which assure the integrity of study data, are described below. In addition to preparing and then locking data sets that report results from this project, the data manager will analyze results of the annual rater inter-rater reliability assessments. He will also oversee and execute procedures for data security and access, data quality control, storage, and back-up, and will provide periodic reports of accrual, follow-up, and summary statistics as required by the Data Safety Monitoring Board (DSMB).

Data Integrity: Sites will send original copies of de-identified hard data to the data management team at Cornell by overnight shipping every second week. Sites will retain hard copies of these records. The de-identified hard data will be stored in a locked filing cabinet stored in a locked office to further protect subject anonymity. Results will be published as group data without the use of characteristics that would identify individual subjects. Data auditing, entry and quality control will be carried out at Cornell under the supervision of the data management team. The Cornell data management team has many years of experience in data management and coordination of multi-study, multi-site research projects. The data management team has developed an infrastructure that supports the design of and standardization of databases, data entry, data quality control, and preparation of data for statistical analysis. This expertise will be applied in implementing a system that assures the quality of data entry, storage, verification, and validation, and the reporting of data from this study. This will involve consultation with the study's statistician on the design of study databases and other issues related to the study's data management infrastructure. Emphasis will be given to incorporate database components that were used in STOP-PD because the proposed project is also a randomized controlled trial and uses variables that overlap with those used in STOP-PD. This system will also support the tracking of subjects and data at the individual sites. The Cornell data management team will maintain regular communication with site study coordinators to ensure that data collection is complete and accurate. Regularly scheduled, and as needed, communications between the inter-site project coordinator at Cornell, the data manager, and raters and investigators will be used to clarify inconsistencies and ambiguities in data submitted to Cornell.

A project team dedicated to the study led by the study's statistician will oversee all data management and quality assurance procedures, including coordination across sites. All data management resources used at Cornell in the multi-site and single site studies conducted through the Geriatric Institute will be made available to the proposed study. Data management resources will be devoted to overall quality assurance including: maintaining interview schedules and subject tracking, monitoring scale completion, monitoring the accuracy of scale completion and data entry, analyzing results of inter-rater reliability assessments as instructed by the investigators, and developing and maintaining a dataset for use in analyses that have been approved by the Publications Sub-Committee. The data management staff has automated many data management steps, which will facilitate the development of the database and the standardization of databases and procedures across sites. For example, several steps in database design have been automated previously so that when the database of the proposed study is set up, it will have a standard structure, with all tables set up the same way and variables named following a standard convention. The data management team has also developed a set of standards and procedures for documentation of data sets produced for statistical analysis.

To assure that the entry of subject data is accurate, the data management team audits 100% of the data turned in by research assistants and investigators for necessary identifiers, item completeness and consistency of major clinical indicators. Audits include such factors as diagnosis, depression severity (Ham-D) and whether the severity score is consistent with the diagnosis. Data are audited and tracked by scale. To date, the auditing system at Cornell has tracked over 170,000 individual scales representing all studies conducted at Cornell. These data have been contributed by users of the Advanced Center for Services and Intervention Center (Dr. Alexopoulos); through various R24 research infrastructure grants (Dr. Meyers and Dr. Bruce); through the two U01 grants led by Cornell investigators (Dr. Meyers and Dr. Young); and by investigators conducting R01s at Cornell. When problems are found (approximately 6% of scales), the instrument is returned to the interviewer. Also, errors are entered into a report, which is then sent to the relevant site's coordinator. The coordinator is responsible for ensuring the errors are corrected within two

weeks. Also, reports on error rates are prepared at regularly scheduled intervals. The data management team tracks this information over time to assure that all data errors are corrected and that the error rates of individual interviewers and individual sites are consistently low over time. If error rates are not acceptable, the inter-site project coordinator intervenes and additional training is provided to problematic raters with interventions made by site principal investigators and the overall principal investigator as needed. The audit system also keeps track of the physical location of all data. As scales are entered, a proportion (10%) will be randomly chosen and flagged for double entry. When the data entry person finishes entering such a scale, he or she will receive a message that the scale must be entered a second time, and this second entry must be completed before any further tasks are allowed. The system automatically checks each item and tabulates and records error rates. This system is completely automatic and the current overall data entry error rate is 0.27%.

4.2 RISKS TO HUMAN SUBJECTS

4.2.1 Human Subjects' Involvement and Characteristics: This proposed multi-centered study will involve four research sites, with each site recruiting 82 patients 18 years or older with non-bipolar major depression with psychotic features (PD). Patients meeting the study entry criteria will be recruited from inpatient, partial hospitalization, and outpatient programs at participating sites. Participants who begin the study as inpatients can continue to participate in the study on an ambulatory basis as determined by the participant's clinical state. Potential participants will be identified using the same broad approach that was employed in STOP-PD and that adhered to local IRB requirements and privacy legislation: daily screening (on week days) of inpatient units, partial hospitalization programs, psychiatric emergency rooms and outpatient clinic referrals, and referrals from clinical staff.

Inclusion criteria

- 1) Aged 18-85 years, inclusive;
- 2) Diagnosis: DSM-IV non-bipolar major depression with psychotic features, established through both a clinical interview by a research psychiatrist and the subsequent administration of the SCID-IV by a research associate
- 3) Score of ≥ 3 on the delusion severity item of the SADS ('delusion definitely present'), with or without hallucinations on the SADS hallucination item;
- 4) Score of ≥ 2 on any of the three conviction items of the DAS (the participant is certain a belief is true and does not change the belief in response to reality testing by the interviewer);
- 5) 17-item Ham-D score of ≥ 21 .

Exclusion criteria

- 1) Current or lifetime DSM-IV criteria for schizophrenia, other psychotic disorders (e.g., schizoaffective disorder, delusional disorder, brief psychotic disorder, and shared psychotic disorder), or mental retardation, or meeting DSM-IV criteria for current brief psychotic disorder, body dysmorphic disorder, or obsessive-compulsive disorder;
- 2) Current or lifetime DSM-IV criteria for bipolar affective disorder;
- 3) History of DSM-IV defined substance abuse or dependence, including alcohol, within the last three months;
- 4) DSM-IV defined Alzheimer's dementia, vascular dementia, or dementia due to other medical conditions, or a history of clinically significant cognitive impairment prior to the index episode of depression, and/or a mean score of ≥ 4 on the 26-item IQCODE. The IQCODE will be used to screen for clinically significant cognitive decline that began prior to the index episode of PD. The IQCODE is not significantly confounded by age, education, or premorbid intelligence.¹¹⁰ Persons with a mean total IQCODE ≥ 4 will be excluded from participation in the study; this cut score has been found to have a sensitivity of 84-93% and specificity of 88-94% in screening for dementia in general, psychiatric, and medical populations of older adults.^{109,110,155,156}

- 5) Type 1 diabetes mellitus (defined as insulin-dependent diabetes mellitus with onset < 35 years of age and/or diabetes mellitus that has been complicated by a prior documented episode of ketoacidosis¹⁵⁷)
- 6) Acute or unstable medical illnesses (e.g., delirium; metastatic cancer; unstable diabetes; decompensated cardiac, hepatic, renal or pulmonary disease; stroke; or myocardial infarction) within the last three months; current abnormal serum free T4; current abnormally low serum vitamin B12 or folic acid level; medical conditions and/or medications for which psychotic or depressive symptoms can be a direct manifestation (e.g. Cushing's disease, high-dose systemic corticosteroids, L-dopa); neurological disease associated with extrapyramidal signs and symptoms (e.g. Parkinson's disease); epilepsy, if the person has had one or more grand mal seizures in the past 12 months;
- 7) The need for treatment with any psychotropic medications other than sertraline, olanzapine, or lorazepam; or with an anticonvulsant medication with mood-stabilizing properties (carbamazepine, lamotrigine, valproic acid);
- 8) Current pregnancy or a plan to become pregnant during the duration of the study in woman of childbearing age; breast-feeding in woman with infants;
- 9) A clearly documented history of being unable to tolerate sertraline and/or olanzapine, including having had an untoward previous reaction to sertraline such as significant bradycardia (heart rate of <50 bpm) or development of the syndrome of inappropriate antidiuretic hormone secretion with a serum sodium of 129 mmol/L or below;
- 10) History of non-response of the index episode of PD to at least a 6-week trial of ≥150mg/day sertraline combined with ≥ 15mg/day olanzapine;
- 11) Patients showing ongoing improvement in the index episode of PD with treatment, other than sertraline and olanzapine, initiated prior to the study;
- 12) Sufficiently ill to require immediate ECT (e.g., imminent risk of suicide, refusing to eat or severe malnutrition, catatonic)

Rationale for inclusion and exclusion criteria

- 1) Age criterion: Excluding children below the age of 18 years from this study of PD is justified on ethical and scientific grounds. We do not know enough about the efficacy of these medications or their tolerability in children at target doses to justify including children.
- 2) Excluding patients with bipolar affective disorder: Persons with bipolar affective disorder require continuation and maintenance treatment with a mood-stabilizing medication to lessen the risk of relapse or recurrence of mania, hypomania, or depression. Antidepressant medication alone is not recommended in the continuation or maintenance treatment of bipolar disorder. As a result, we exclude patients with a known history of bipolar disorder, because it would not be ethical to discontinue olanzapine, which has efficacy as a mood-stabilizer in bipolar disorder, in these individuals.
- 3) Depression severity criteria: Only subjects with moderately severe to severe depression will be included to increase the likelihood that delusions are a symptom of PD, rather than of schizophrenia or another psychotic disorder with secondary depression.
- 4) Requiring delusions, with or without hallucinations: The rationale for requiring delusions, whether or not hallucinations are present, is based on the infrequency of hallucinations alone (that is, without delusions) in PD.^{158,159} Psychotic patients with hallucinations only, who do not have delusions, are more likely to be suffering from another disorder, such as schizophrenia, schizoaffective disorder, brief psychotic disorder, or a toxic-metabolic encephalopathy, as a cause of their psychotic symptoms. Thus, the requirement of delusions will facilitate diagnostic precision.

5) Exclusion of recent substance abuse or dependence: The DSM-IV criteria for substance abuse or dependence defines these disorders as a maladaptive pattern of substance use occurring within a 12-month period. We elected to use a narrower exclusion criterion of abuse (within the past 3 months) in order to allow participation by subjects with histories of substance abuse or dependence problems that could be secondary to their mood disorders. However, we decided to exclude individuals in whom very recent substance abuse or dependence might be contributing to the mood or psychotic symptoms. A valid and reliable diagnostic distinction between unipolar PD and a substance-induced mood disorder with psychotic features can not be made in the presence of current substance abuse. Participants with a secondary psychotic depression may have a different treatment response and longer term outcome than those with primary PD. However, allowing participation by patients with histories of substance abuse or dependence more than three months earlier broadens the inclusion criteria to more closely approximate patients seen in 'real world' settings.

6) Patients with schizophrenia, schizoaffective disorder, and other psychotic disorders are excluded, because the focus of this study is on major depressive disorder with psychotic features, not 'primary' psychotic disorders with associated depression. Current body dysmorphic disorder and obsessive-compulsive disorder are excluded because the ideation and phenomenology associated with these disorders may be difficult to reliably distinguish from PD.

7) Persons with dementia are excluded for the following reasons:

a) delusions and depression may be symptomatic manifestations of dementia. The pathophysiology, treatment response, and course of these symptoms of dementia may differ from those of PD.¹⁶⁰ Moreover, non-delusional confabulations are a frequent symptom of dementia and may be difficult to reliably distinguish from delusions;

b) dementia may affect a person's ability to reliably and accurately report the presence and course of symptoms, which could affect the validity of ratings of outcome.

8) Persons with Type 1 diabetes mellitus are at risk of ketoacidosis if they become hyperglycaemic, whereas ketoacidosis is a very rare event in persons with Type 2 diabetes mellitus.¹⁵⁷ Therefore, to avoid the potential risk of ketoacidosis precipitated by olanzapine-associated hyperglycemia, persons with Type I diabetes will be excluded from the study. In STOP-PD, no more than 7 of the 259 participants had Type 1 diabetes; therefore, we do not anticipate that this exclusion will have a significant impact on recruitment, the aims pertaining to metabolic changes, or generalizability of the study's findings.

9) Acute or unstable medical illnesses may prevent participants from tolerating the acute trial target doses of study medications, interfere with subjects' ability to complete the study, and/or contribute to psychiatric symptomatology. We will, however, include subjects with stable chronic physical illness, to examine the interaction between chronic medical burden, duration of treatment with olanzapine, and risk of relapse/recurrence.

10) Exclusion of women who are pregnant, plan to become pregnant or are breast-feeding. Sertraline and olanzapine are not specifically known to harm the fetus, but the data are limited. As a result, to err on the side of caution, pregnancy is an exclusion criterion. Sertraline is present in breast milk and, therefore, may be transmitted to breast-feeding infants.

11) Exclusion of patients with a history of treatment resistance to an adequate trial of combined sertraline and olanzapine during the index episode is justified on ethical and scientific grounds. It would not be ethical to include patients whose current episode of depression had previously failed to respond to an adequate trial of the same treatment used during the acute phase of the study. Moreover, the inclusion of such patients would likely reduce the overall frequency of remission and near remission of the acute phase of the trial, thereby reducing the potential pool of patients available to enter the RCT. We expect that this exclusion criterion will have little impact on recruitment of participants to the acute phase of the study: in STOP-PD, only 5% of participants had received at least a three-week trial of adequate doses of combined treatment with any antidepressant and antipsychotic medications during the index episode prior to the study.¹⁶¹

12) Exclusion of patients considered at imminent risk for suicide and/or whose symptoms are severe enough to warrant immediate treatment with ECT is appropriate on ethical grounds.

4.2.2 Sources of Materials: Following written informed consent, the research materials will come from 3 sources:

- 1) Interviews of patients, and when indicated, other reliable informants. Interviews and rating scales described in Section 5.4 will be administered by trained research associates to patients. In the case of some scales, collateral information will also be obtained from a reliable informant who is familiar with the participant.
- 2) Medical and pharmacy records: information from inpatient and outpatient medical records will, at times, be used to supplement information obtained from patients and reliable informants, to facilitate completion of rating scales. In addition, information from pharmacy records may at times be required for completion of the ATHF, which rates the type and adequacy of antidepressant and antipsychotic treatment received by participants during the index episode of depression.
- 3) Blood tests: tests for genetic analyses, metabolic analyses, and sertraline and olanzapine plasma levels, will be based on blood samples obtained from participants.

4.2.3 Potential Risks: The most common side effects associated with the use of sertraline and olanzapine in STOP-PD (occurring in more than 10% of participants) were: weight gain, somnolence/sedation, gastrointestinal symptoms, experiencing at least one fall, and orthostatic dizziness. In addition, elevated levels of blood glucose, cholesterol and triglycerides have been associated with olanzapine. Olanzapine, along with other atypical antipsychotics, has been associated with a slight increased absolute risk of cerebrovascular events (mainly TIAs) in persons with severe dementia. However, we will not be including persons with dementia in this study. Users of antipsychotic drugs have an increased risk of mortality compared with non-users of this class of drugs: in the case of users of olanzapine, the increased absolute risk across diagnostic groups has been estimated at 0.9% over 2-3 years of current use.¹⁶² We will explicitly discuss the potential mortality risk in the consent process. Blood tests may cause some minor discomfort or bruising.

Severe depression increases the risk of suicidal ideation and behavior. Participation in the study will likely reduce this risk, but this is not guaranteed. The FDA recommends close observation of people taking antidepressant medication, including sertraline, for worsening depression or the emergence of suicidal thoughts or plans. As described in Section 3.9.5 participants will be closely monitored for suicidal ideation and behavior.

Discontinuation of antipsychotic medication in PD may possibly be associated with an increased risk of relapse and recurrence of PD, although this is not known. We have estimated the overall risk of relapse to be approximately 25% during the course of the RCT. Cases of relapse will be treated promptly.

Alternative Treatments: ECT can be used to successfully treat PD. However, ECT is associated with its own risks, including cognitive impairment, cardiac arrhythmias, musculoskeletal injury, damage to teeth, and very small risk of death. Although ECT is a successful acute treatment for PD, it is associated with up to a 50% risk of relapse of PD in the 6 months following discontinuation of ECT. Antidepressant medications other than sertraline and antipsychotic medications other than olanzapine are used in clinical practice to treat PD. However, as discussed in Section 3.5, olanzapine is the only atypical antipsychotic with evidence of efficacy in the treatment of PD.

4.3 ADEQUACY OF PROTECTION AGAINST RISKS

4.3.1 Recruitment and Informed Consent

Recruitment: It is imperative to screen, recruit and treat study participants as quickly as possible. This is emphasized because patients with PD are frequently recruited from inpatient services and these units are under pressure to begin treatment rapidly. The study coordinator and principal investigator, both of whom will be on beeper call, will aim to ensure that potential subjects are screened by the research associate within 24 hours of admission to a clinical service, or as close to that time frame as possible for patients admitted on weekends. Each principal investigator has considerable experience in recruiting and studying patients with PD. In addition, by maintaining close communications with the admitting personnel of participating hospitals, the principal investigator and study coordinator will be aware of scheduled admissions that may meet inclusion criteria before they arrive at the hospital. The research associate will discuss potential subjects with the treating physician about potential suitability. The study coordinator and principal investigator will be contacted if the treating physician agrees that the patient is suffering from a unipolar delusional PD and the patient has

agreed to meet with the research team. This will facilitate rapid screening and scheduling of a meeting to assess eligibility and of capacity assessment soon after admission. For scheduled admissions, the research team will attempt to schedule a preliminary meeting with the patient and accompanying family members at the time of admission, if the treating physician and the patient agree to the meeting.

Informed Consent: PD may impair a person's capacity to consent to participate in a research study. To recruit people who are representative of the population being studied, the study will allow people who do not have the capacity to give informed consent to participate in the open-label phase of the study (acute and stabilization), as long as they assent to participate and informed consent is obtained from a surrogate decision maker. Subjects who are eligible for the randomized phase must have achieved sustained remission or near remission by the end of stabilization and will therefore need to be capable of giving informed consent in order to participate in the randomized controlled trial.

We are not able to provide uniform criteria for appointment of a surrogate, because sites in the proposed study differ in their local requirements for how surrogates are selected. The Cornell IRB, in accordance with New York State regulations, stipulates that incapable research participants must have the capacity to know that they are appointing a surrogate and must be aware of their relationship to the surrogate they are appointing. On the other hand, IRBs of the other sites of the proposed study stipulate a priority order in which potential surrogates may be approached, although the details of the assigned order differ between sites. We will ensure that the surrogate appointment process meets all local requirements and that the process to be used at each site is approved by the local IRB.

To protect the rights of people whose decision making capacity may be impaired, those who are deemed capable of consenting to treatment by the research psychiatrist will have a second capacity assessment. The second assessment will be completed by either a licensed mental healthcare professional (psychiatrist, psychologist, or mental health social worker) who is independent of the study or by a research associate's administration of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR).¹⁶³ The MacCAT-CR is a semi-structured interview for assessment of capacities related to consent to research. It has been found to be a valid measure of capacity to consent in persons with psychosis. The principal investigators of this study were trained in the use of the MacCAT by Dr. Paul Applebaum, who developed the instrument; they have several years of experience in the use of this instrument in STOP-PD. Because time is of the essence in starting treatment in a study of PD, use of the MacCAT-CR will allow for situations where an independent healthcare professional cannot provide a timely capacity assessment. If the second capacity assessment suggests that the person lacks capacity to consent, surrogate consent must then be obtained.

All participants for whom surrogate consent is obtained at the start of the study will have their capacity to consent to participate in the study re-assessed at the start of the stabilization phase. Given that participants will have experienced remission of psychosis and remission or near remission of depressive symptoms by the start of stabilization, we expect that incapable participants will have gained capacity to consent to the study by that stage. Once a participant is deemed capable of consenting to treatment by the research psychiatrist, s/he will have a second capacity assessment as described in the paragraph immediately above. If the second capacity assessment finds that the participant has capacity to consent to participate in the study, the participant will then be asked to provide written informed consent.

Participants will have their capacity assessed by the research psychiatrist at the end of 8 weeks of stabilization to determine whether they have capacity to give informed consent to participate in the randomized controlled trial. If the participant has capacity to consent to participate in the randomized trial, the participant will then be asked to provide written informed consent. Capacity to consent to the randomized trial will be required for subjects to participate in that phase of the study.

4.3.2 Protections Against Risks

Non-Response or Worsening of Depression: Patients who do not meet the study's remission criteria after 12 weeks of acute treatment with sertraline and olanzapine will not be eligible to participate in the stabilization phase and the RCT. These patients will leave the study at the end of 12 weeks of acute treatment and be

treated on a 'doctor's choice' basis by an attending physician. Participants who are judged to have significant clinical worsening during the acute or stabilization phases of the study will be withdrawn from the study, so that treatment can be administered under routine clinical conditions by an attending physician. Significant clinical worsening will be operationalized as a CGI change score of 6 or 7 ('much worse' or 'very much worse').

Monitoring During and Following Antipsychotic Discontinuation: Study participants will have in-person research assessments on a weekly basis during the first 8 weeks of the RCT. These weekly assessments will cover the period of olanzapine taper and its immediate aftermath, thereby providing intensive follow-up of patients during this period. In addition, for the remainder of the RCT, participants will be assessed every 2 weeks (alternating research and clinical assessments) to monitor for the possibility of clinical worsening. If a participant experiences clinical worsening, he/ she will be seen on an urgent basis by a research psychiatrist associated with the study, to determine if the participant meets criteria for relapse or whether a change in olanzapine/placebo dose or the use of lorazepam is indicated.

Management of Relapse: Patients who meet relapse criteria will be referred to a psychiatrist who is not affiliated with the study, who has agreed to see patients within 48-72 hours of referral. Alternatively, patients can be referred for acute psychiatric hospitalization, if deemed appropriate by the study psychiatrist. Based on the frequency of relapse postulated for the study, we estimate that there will be an average of 3 cases of relapse per year per study site.

Management of Suicide Risk: Lifetime suicidal ideation and behavior will be assessed with the SCID. Suicidal thoughts, plans, and attempts during the study will be rated with the SSI. Patients at 'imminent risk' of suicide will not be enrolled in the study. Patients at 'high risk' of suicide must start the study as an inpatient. High risk of suicide is operationalized as any one of the following: 1) a current suicide plan; 2) a suicide attempt during the index episode; 3) one or more lifetime serious suicide attempts, defined as attempts requiring inpatient medical treatment. Suicidal ideation and behavior will be rated with the SSI at each study visit. As outlined in Section 3.9.5, participants will be seen weekly by a research psychiatrist for the first 6 weeks of the Acute Phase of the study, and then every two weeks for the remainder of the Acute Phase and the Stabilization Phase. If a participant has a current suicide plan or has had a current suicide attempt, he/she will be removed from the study and the research psychiatrist will make a clinical decision about the most appropriate course of action, including whether the patient requires immediate hospitalization. In the case of participants who are found to have a current suicide plan or had a current suicide attempt based on the research associate's clinical phone assessment, the research psychiatrist, who will be available by pager, will be immediately informed by the research associate and the psychiatrist will then talk on the phone with the participant. The psychiatrist will then make a decision about whether the patient should be referred for immediate psychiatric hospitalization or whether it is safe for the participant to be seen for a research termination visit, and subsequent clinical management, the following business day.

If a participant has current suicide ideation (as indicated by a score of 1 or 2 on items #4 or 5 of the SSI) but no current suicide plan or attempt, he/she may remain in the study at the discretion of the research psychiatrist, based on the psychiatrist's clinical assessment of the participant's suicide risk. If the participant remains in the study, he/she will be followed in-person by the research psychiatrist on a weekly basis to monitor the participant's safety, to decide whether ongoing participation in the study is appropriate, and, if indicated, to adjust the dosages of study medications as allowed by the treatment protocol. These weekly clinical visits, which will be in addition to the scheduled research assessment visits, will continue until the participant no longer has suicidal ideation or is removed from the study and managed 'clinically'.

Adverse Effects: Side effects will be systematically monitored at each assessment and visit (Section 3.9.5). As described in Section 3.9.9 and the appended Pharmacotherapy Protocol, reduction in dosing of sertraline and olanzapine, to specified minimum dosages, will be allowed during the acute and stabilization phases and RCT, if necessitated by clinically significant side effects. In addition, bztropine can be prescribed if clinically significant extrapyramidal side effects do not adequately improve with a reduction in dose of olanzapine (see Section 3.9.8 and appended Pharmacotherapy Protocol). Participants who are withdrawn from the study will be treated on a physician choice basis by their attending physician.

Monitoring of metabolic effects: As described in the Schedule of Events (Section 3.9.5), metabolic parameters will be measured at week 4 of the Acute Phase and thereafter every 8 weeks of the study. If a participant develops clinically significant elevations of fasting serum glucose(>100mg/dL), triglycerides(>150mg/dL), total cholesterol(>200mg/dL), and/or LDL cholesterol(>130mg/dL), s/he will be referred to his/her primary care physician (PCP) for further assessment and management of the metabolic finding(s), including a discussion about the risks and benefits of ongoing participation in the study. If a participant does not have a PCP, the research psychiatrist will refer the patient to a PCP who has agreed to see patients enrolled in the study.

Confidentiality of Information: The consent form will stipulate that participants' information will remain strictly confidential, with access limited to research staff, and, if indicated, local IRBs, the NIMH-run DSMB, and state or federal regulatory personnel. No one but study personnel will have access to the lists linking participant's names to code numbers. All information pertaining to participants will be coded to protect participants' identities and will be stored in locked cabinets in locked offices of the investigators. Publications or presentations of findings will not include information that identifies participants.

Sharing of Genetic Data: We plan to collaborate with the NIMH Center for Genetic Studies, a facility operated under federal contract to manage data and establish high-quality cell lines for human genetics projects supported by NIMH. Our biomaterials and the associated clinical data will be incorporated with other such data and biomaterials as part of the NIMH Human Genetics Initiative. NIMH will then follow existing procedures and protocols and distribute these data and biomaterials to qualified researchers in the wider scientific community. Please see Section 15 (Resource Sharing), for the detailed plan of sharing of biomaterials and data with the NIMH Center for Genetic Studies.

We are in receipt of the NIMH-written model consent form pertaining to the sharing of genetic data. We will utilize this consent form, which will clearly stipulate: (1) disclosure that biological materials (DNA and cell lines) and clinical data will be stored at a central data management/laboratory facility, as part of a national resource of data and materials distributed by NIMH for the genetic analysis of the disease under investigation; (2) assurance that such data will be provided to a central facility without personal identifiers; (3) disclosure that analyses of these data will be conducted by other scientists currently not included within the current research team; and (4) disclosure that there is no plan to provide subjects with any financial benefits from commercial products derived from the data. We will provide NIMH with our approved consent form prior to the start of the proposed study. Any data-sharing with investigators outside of Cornell University, the University of Massachusetts, the University of Pittsburgh, and University of Toronto will involve making all of shared data anonymous (so that no identifiers could link data back to subjects), per IRB policy.

4.4 POTENTIAL BENEFITS

The benefits to participants will include:

1. Evaluation of their mental and physical health;
2. Ongoing monitoring of their clinical condition;
3. Treatment with a medication regimen that has been shown to be efficacious in the acute treatment of PD;
4. The possibility that symptoms of PD will improve with treatment.

The potential benefit to society is determining whether continued antipsychotic medication prevents relapse of PD.

4.5 IMPORTANCE OF KNOWLEDGE TO BE GAINED

It is not known whether antipsychotic medication needs to be continued once an episode of PD has responded to combined antidepressant-antipsychotic treatment. This issue is of tremendous clinical importance. On the one hand, the unnecessary continuation of antipsychotic medication exposes a patient to adverse effects, some of which have considerable public health significance. On the other hand, premature discontinuation of antipsychotic medication has the potential risk of early relapse of a severe, disabling disorder. Addressing these issues will be of major public health importance. In our view, given the precautions that will be taken in this study, the likely benefits to participants and society outweigh the potential risks.

4.6 DATA AND SAFETY MONITORING BOARD (DSMB)

A NIMH-run DSMB oversaw the STOP-PD U01 to ensure the safety of participants and the validity and integrity of the data. Our understanding is that this grant, submitted as a Collaborative R01, will be converted to a U01 upon funding. As a result, members of the DSMB will be chosen by NIMH. The responsibilities of the DSMB will include, but not limited to, the following:

1. Review of protocols, consent procedures, consent forms, and safety plans prior to initiation of the study;
2. Monitoring the progress of the study, including recruitment and retention of participants, adverse events, serious adverse events, reasons for participant withdrawal, adherence to the time line of the study, quality of data, and protocol violations;
3. Make recommendations about the continuation, modification, or termination of the study, based on the balance of adverse events and beneficial outcomes;
4. Request addition data, as needed.

The responsibilities of the overall principal investigator of the study (Dr. Meyers), in collaboration with the study statistician/methodologist, in relation to the DSMB, will include, but not be limited to, the following:

1. Preparation of quarterly reports of all adverse events, SAEs, participant recruitment, and reasons for participant withdrawal;
2. Respond to questions and recommendations from the DSMB, based on their review of the quarterly reports, or at any other time as needed;
3. Inform the DSMB and the Coordinating Center IRB within 48 hours of any SAE;
4. Send blinded data to the DSMB for DSMB-performed interim analyses, if requested by the DSMB;
5. Send the DSMB a final report of the study's findings;
6. In addition, the principal investigators of each study site will be responsible for reporting any SAE to the Cornell IRB within 48 hours, as well as reporting the SAE to their specific site IRB, based on local IRB requirements.

a. CLINICAL TRIALS.GOV

This is a renewal of the NIMH-funded U01 'Acute Pharmacotherapy of Unipolar Psychotic Depression', which has a clinical trials.gov identifier NCT00056472.

5. INCLUSION OF WOMEN AND MINORITIES

5.1 RECRUITMENT OF WOMEN AND MINORITIES

Eligible patients will be offered the opportunity to participate regardless of gender or minority status. Considering that 50% of subjects will be elderly patients, and considering the gender distribution of PD, the proportion of females to males will approximate 2:1 at all sites. The composition of the study sample will reflect the racial diversity of patients seen at the four research sites. Although sites vary somewhat by racial composition, the overall distribution of major ethnic and racial groups will assure all groups are represented as outlined in the Targeted/Planned Enrollment Table.

Cornell Westchester serves a large county that reflects the socioeconomic diversity of the United States. For example, Yonkers, the third largest city in New York State, has a more indigent population and has higher proportions of Hispanic and African American persons, while northern Westchester is comprised of semi-urban, suburban, and rural communities that tend to be over-represented by Caucasians and more affluent individuals. Among subjects recruited from Westchester, 13% are anticipated to be African American and 13% Hispanic; these percentages may, however, turn out to be higher, because of the greater prevalence of minorities among New York City residents recruited via Payne Whitney Manhattan.

The University of Pittsburgh Medical Center serves the City of Pittsburgh and the surrounding Allegheny County. We anticipate that recruitment in the proposed study will reflect the demographic diversity of the City of Pittsburgh [67% white, 27.1% African American, 2.8% Asian, 1.3% Hispanics with minimal representation of

other ethnic minorities] and the City of McKeesport [72% white, 25% African American, 0% Asian, 1.5% Hispanic with minimal representation of other ethnic minorities.]

The University Health Network serves patients from the greater Toronto area. Toronto is one of the world's most ethnically diverse cities, with approximately 40% of its population classified as of visible minority. 34% of patients recruited at the Toronto site of STOP-PD were Asian, Black, or Hispanic. We anticipate that recruitment in the proposed study will continue to reflect Toronto's racial and ethnic diversity.

At the University of Massachusetts Medical School, we expect 15-20% of the subjects recruited to be Hispanic. The 2000 United States Census indicated the Hispanic population of Worcester County to be 15.2%, a 52% increase from 1990 to 2000.

5.2 CULTURAL COMPETENCE OF STUDY PERSONNEL

Investigators, research coordinators, and research associates will participate in training in cultural competence, as part of the study's personnel training. These personnel will be required to complete the five core modules of the Curriculum in Ethnogeriatrics, an internet-based resource for education and training in cultural competence [<http://www.stanford.edu/group/ethnoger>] supported by the Bureau of Health Professions, Health Resources and Services Administration, U.S. Department of Health and Human Services. The five modules cover the following topics: i) an introduction to, and overview of, culturally-competent care of elders, ii) patterns of health risk among people from diverse ethnic backgrounds, iii) culturally-based health beliefs, iv) knowledge and skills needed to provide a culturally competent assessment, and v) cultural issues in the delivery of health care after assessments are completed, including health promotion, informed consent, treatment, and working with families. The Curriculum in Ethnogeriatrics also has 12 ethnic-specific modules that can be used as an additional resource when needed. Although this educational tool has a focus on the older population, which is very pertinent to the proposed study, its principles and themes are also applicable to younger and middle-aged adults.

Data from STOP-PD are consistent with our research group having culturally competent attitudes and skills. In STOP-PD, 84.2% of participants were white, 11.2% were African American or black, and 4.6% were Asian; 11.6% of participants described themselves as Hispanic or Latino. Based on census data, these percentages were comparable to the racial and ethnic make-up of the U.S. population at the time that the study was conducted. Rates of completion at Weeks 6 and 12 of the 12-week study were highly comparable between racial and ethnic groups (see Table 5). Thus, these data show that we were successful in both recruiting and retaining minorities in STOP-PD.

Table 5: Percentage of Participants Completing the 12-Week STOP-PD Study by Ethnicity and Race

Race and Ethnicity	Number of Randomized Participants	% Completers (Week 6)	% Completers (Week 12)
Asian	12	75.0	50.0
Black or African American	29	75.9	51.7
White	218	74.8	55.5
Hispanic or Latino	30	80.0	53.3
Not Hispanic or Latino	229	73.8	55.0

6. RESOURCE SHARING

6.1 THE STUDY'S DATABASE

Once the main findings of the study have been accepted for publication, the database will be made available to clinical investigators and others as requested, The public use database will be de-identified using HIPAA

standards and will consist of several data files including baseline data and outcome assessments. Each data file will be made available as formatted SAS datasets (other upon request). The permanent SAS dataset format has been adopted on the basis of SAS's widespread acceptance in the scientific community, strong data management capabilities, and robust statistical procedures. The permanent SAS data files are stored on one server at Weill Cornell Medical College and archived for all data transfers including transfers for data sharing. The SAS data files can be copied to a CD for transfer off site or can be electronically transferred via the secure study website. SSL encryption methods allow for a secure internet transfer. A complete data dictionary listing of all data validation procedures (rules) and labels is also included in the transfer for reference. Those wishing access to the data will submit a written request to the overall study Principal Investigator (Dr. Meyers), specifying the purpose for which the data will be used and the desired transfer method. Publications reporting the study's findings will be listed on the ClinicalTrials.gov website, consistent with NIH requirements.

6.2 SHARING OF BIOMATERIALS AND DATA WITH THE NIMH CENTER FOR GENETIC STUDIES

We plan to collaborate with the NIMH Center for Collaborative Genetic Studies ("the Center"), a facility operated under federal contract to establish high-quality cell lines and manage data for human genetics projects supported by NIMH. Our biomaterials, and the associated clinical data, will be incorporated with other such data and biomaterials as part of the NIMH Human Genetics Initiative. NIMH will then follow existing procedures and protocols to distribute these data and biomaterials to qualified researchers in the wider scientific community. Yin Yao Ph.D., Director of the Genetics and Genomic Research Resources Program at NIMH, has expressed her willingness for us to access the Center (personal communication, 11/13/2009) and has read and approved the data sharing plan below (personal communication, 1/12/2010).

6.2.1 Biomaterials: Whole blood on all consenting participants will be sent directly to the Center for the generation of cell lines and extraction of DNA. Blood samples will be sent as they are collected, on an ongoing basis during the proposed 38 months of recruitment. Blood samples will be shipped using the Center's established protocols that are designed to minimize trauma (e.g. excessive heating or freezing). DNA will be shipped from the Center to Dr. James Kennedy's genetics laboratory at CAMH in Toronto, within 4 months of the blood sample being received by the Center. Blood samples sent to the Center will be identified by code number only. We anticipate that approximately 10 blood samples per month during the 38 months of recruitment will be sent by our study personnel to the Center. Verified genotypic data will be provided for release as stated below under "Data and Biological Materials Dissemination".

6.2.2 Clinical Data: Verified clinical data will be electronically submitted from the study's coordinating center at Weill Cornell Medical College to the Center every 6 months. As described in detail in other sections of the grant application, the following issues will be addressed to ensure and check the quality of data:

Structured Diagnostic Criteria. The diagnosis of non-bipolar major depression with psychotic features (PD) will be established according to DSM-IV criteria.

Comprehensive Phenotypic Assessment. The diagnosis of PD will be based on a clinical interview by a research psychiatrist associated with the study, followed by an research associate's administration of the Structured Clinical Interview for DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; SCID-IV-TR).¹⁰³ As a third line of assessment, diagnostically unclear or complex cases will be discussed by the principal investigators to reach a consensus about the patient's eligibility for the study. In addition, as described in Section 3.9.5, participants will be well characterized at baseline in terms of demographic characteristics, severity of depression, type and severity of psychosis, suicidal ideation and behavior, severity of concomitant anxiety, cognitive function, medical burden, and history of treatment resistance.

Rater Training and Reliability. As described in Section 4.1.6, all raters will participate in formal training prior to assessing participants for the study and collecting data, receive ongoing supervision from study coordinators and research psychiatrists at each site, and participate in weekly conference calls led by the inter-site Project Coordinator to address quality assurance issues. Inter-rater reliability on primary outcome measures will be evaluated and addressed on an annual basis. Inter-rater reliability assessments performed during each year of the 5-year STOP-PD yielded ICCs of 0.93-0.98 for the GRID HAM-D total score and 0.69-0.84 for the conviction dimension of the DAS, demonstrating good reliability for these primary measures.

Computerized Database and Data Management. The data management center at Cornell has an extensive, fully-functioning computerized database to manage all data derived from the proposed study. Procedures for ensuring data integrity are described in detail in Section 4.1.6. To date, the data auditing system at Cornell has tracked over 170,000 individual rating scales over a period of more than 20 years.

6.2.3 Data and Biological Materials Dissemination: Dissemination of phenotypic and genotypic data will occur at the points in time stipulated below:

- Verified diagnostic data: Will be submitted to the Center no later than 6 months after generation.
- Remaining verified clinical data: Will be submitted to the Center no later than 6 months after generation.
- Genotype data: Will be submitted to the database of Genotypes and Phenotypes (dbGaP) when manuscripts reporting the results based on these data are accepted for publication or no later than at the end of the award, depending on which occurs first.
- Cell lines and DNA samples: To be negotiated with Center's Program Official.
- Diagnostic and clinical data will be eligible for release by the Center, and genotype data will be eligible for release by dbGaP, 12 months after receipt.

6.2.4 Human Subjects Issues: We are in receipt of the NIMH-written model consent form pertaining to the sharing of genetic data. We will utilize this consent form, which will clearly stipulate: (1) disclosure that biological materials (DNA and cell lines) and clinical data will be stored at a central data management/laboratory facility, as part of a national resource of data and materials distributed by NIMH for the genetic analysis of the disease under investigation; (2) assurance that such data will be provided to a central facility without personal identifiers; (3) disclosure that analyses of these data will be conducted by other scientists currently not included within the current research team; and (4) disclosure that there is no plan to provide subjects with any financial benefits from commercial products derived from the data. We will provide NIMH with our approved consent form prior to the start of the proposed study. Any data-sharing with investigators outside of Cornell University, the University of Massachusetts, the University of Pittsburgh, and University of Toronto will involve making all of shared data anonymous (so that no identifiers could link data back to subjects), per IRB policy.

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APPENDIX 1. PHARMACOTHERAPY PROTOCOL

A1. ACUTE PHASE

After written consent is obtained, psychotropic medications that are not permitted in the study (Section 4.2.1) will be withdrawn over a period of up to 4 days, when feasible, prior to starting study medications. However, withdrawal of anticonvulsant medications with mood-stabilizing properties that are not permitted in the study will be extended to 10 days, and may therefore include the first week of the acute treatment phase. In addition, if a participant experiences withdrawal symptoms associated with the taper of psychotropic medication during the 4-day period, the taper may be slowed and continued over 10 days, which will overlap with the first week of the acute phase treatment. Since one of the goals of the acute phase is to maximize the recruitment of participants to the RCT, it is important to allow flexibility in the rate of withdrawal of preexisting psychotropic medications, to maximize the chance of recruiting and retaining participants. Persons who are taking sertraline, olanzapine, or both medications at the time of signing consent for the acute phase of treatment, where this does not affect eligibility for the study (Section 4.2.1), will remain on these medications, and upon entry to the study will have the existing dosages adjusted, when necessary, to reach target doses, based on the protocol's titration schedule. The only psychotropic medications allowed in the study will be olanzapine, sertraline, and 'as needed' lorazepam; 'as needed' benztpine will be allowed to treat EPSE (see below).

Sertraline and olanzapine will be dispensed in a non-blind, open-label fashion during the acute and stabilization phases of the study. Sertraline will be dispensed in the morning as 50 mg tablets. Olanzapine will be dispensed in the evening as 5 mg tablets. The titration schedule of sertraline and olanzapine, and the target dosages of these medications, will be the same as that successfully employed in STOP-PD. Thus, sertraline will be started at a dosage of 50 mg/day and olanzapine will be started at a dosage of 5 mg/day. On day 4, the dosages of sertraline and olanzapine will be increased to 100 mg/day and 10 mg/day, respectively, as tolerated. On day 7, the dosages of sertraline and olanzapine will be increased to the target doses of 150 mg/day and 15 mg/day, respectively, as tolerated. If a participant experiences side effects during the titration phase, downward titration of one or both medications will be allowed as indicated, and the titration of medications can proceed more slowly. In these cases, however, the goal of titration will be to reach target doses within 14 days of starting the medications.

A1.1 Dosage Adjustments Due to Inadequate Improvement: If there is no improvement or inadequate improvement in psychosis, based on the research psychiatrist's clinical judgment, after 7 days of 15 mg/day of olanzapine, the dosage of olanzapine will be increased to 20 mg/day, as tolerated. This flexibility in dosing will allow for dosages to be used at the maximum dose recommended in the product monograph by 2 weeks of starting treatment. Participants who did not experience at least partial improvement in depressive symptoms (partial improvement defined as a 17-item HAM-D score of below 16) after taking sertraline at a dosage of 150 mg/day for 4 weeks, will have the sertraline dose increased to 200 mg/day, as tolerated.

A1.2 Dosage Adjustments Due to Side Effects: The treating psychiatrist will be allowed to adjust the titration of sertraline, olanzapine, or both if the participant experiences side effects that are troublesome or otherwise clinically significant (e.g., sedation, orthostatic hypertension). In such cases, the titration of both sertraline and olanzapine will be halted, or if clinically indicated, the dosage of one or both medications can be reduced. However, titration to reach the target dose will resume, if and when the side effects resolve. If, after a further attempt at titration, a participant is unable to tolerate 150 mg/day of sertraline or 15 mg/day of olanzapine, the

participant may be maintained on a lower dose of these medications, with a minimum allowable dose of 50 mg/day of sertraline and 5 mg/day of olanzapine.

A1.3 Rationale for Dosing: In STOP-PD, by the end of the second week of treatment, the average daily dose of sertraline was 150 mg/ day, for both younger and older age groups, and the average daily dose of olanzapine was 14 mg in the younger group and 13 mg in the older group. These data indicate the feasibility of aiming for target dosages of 150 mg/day of sertraline and 15 mg/day of olanzapine in both age groups. The target dosages of sertraline and olanzapine are designed to ensure that participants receive therapeutic dosages of these medications early in treatment, in an attempt to facilitate improvement as rapidly as possible. Although sertraline has a flat dose-response curve (Preskorn 1993), meaning that, at a group level, higher doses are not necessarily associated with a higher frequency of response, there are individuals who do require higher doses in order to respond. Thus, in order to maximize the chance of early response in all participants, we elected to increase the dose of sertraline to 150mg/day early in treatment, rather than maintain the dose at a lower level for several weeks, before increasing the dose in non-responders.

Many persons with PD are hospitalized, they are frequently severely distressed by their delusions, and food and fluid intake may be compromised by their psychosis. As a result, it is imperative to treat the psychosis in an expeditious manner. Thus, in patients who fail to show significant improvement in psychosis by the end of 7 days of treatment with 15 mg/day of olanzapine, the dosage will be increased to 20 mg/day, as tolerated.

A1.4 As-Needed Lorazepam: Persons with severe anxiety, restlessness, or insomnia that would prevent them from continuing in the study can be prescribed lorazepam, starting at 0.5 to 2 mg/day, as needed. A maximum daily dosage of 3 mg/day will be allowed during the study, but doses will be kept at a minimum and the lorazepam will be withdrawn as early as possible.

A1.5 As-Needed Benztropine: Among participants who develop clinically significant EPSE, the dose of olanzapine will be reduced by 5 mg increments, to a minimum dose of 10 mg/day, if needed to lessen extrapyramidal effects. However, if problematic EPSE persist, despite the dose reduction of olanzapine, benztropine can be prescribed, to a maximum dose of 2 mg/day. Lorazepam and benztropine will not be administered within the 12 hours prior to administration of cognitive tests, so as not to disrupt cognitive function. The prescription of benztropine will be taken into account in the secondary statistical analyses of EPSE.

A2. STABILIZATION PHASE

When participants meet remission criteria, they will continue with open-label sertraline and olanzapine during the 8-week stabilization phase. Since the goal of this phase is to consolidate stability of remission, adjustment of the doses of study medications will be allowed, if necessitated by clinical worsening or significant side effects. In the case of exacerbation of depressive symptoms, sertraline can be increased as tolerated by 50mg increments every 7 days, to the maximum dose of 200mg/day. Because *sustained* remission of psychosis during the stabilization phase will be required for eligibility for the RCT (Section 3.9.2), participants will leave the stabilization phase if they experience a relapse of delusions or hallucinations as determined by SCID interview. Nevertheless, in the case of participants who experience worsening of worry that is not delusional, olanzapine can be increased as tolerated by 5 mg increments every 7 days, to the maximum dose of 20mg/day. If dosage reductions are necessitated by side effects, sertraline can be decreased by 50 mg increments every 7 days as needed, to a minimum dose of 50 mg/day, and olanzapine can be decreased by 5mg increments every 7 days as needed, to a minimum dose of 5 mg/day.

A3. RANDOMIZED CONTROLLED TRIAL

Participants who meet the study's remission criteria, will be randomly allocated, following completion of the stabilization phase, to either continue olanzapine or switch from olanzapine to placebo (see Data Analysis section for details of the randomization procedure). Randomization assignments will be generated by Dr. Andy Leon, the study's statistician, and sent to the research pharmacist at each site who will dispense study medications. Records of each subject's treatment assignment will be kept at the respective pharmacies and

made available if a clinical emergency occurs. Site principal investigators and their co-investigators will carry beepers to ensure that 24-hour/day coverage is provided for medical emergencies that may arise in study participants.

A3.1 Sertraline: Participants will take open-label sertraline for the duration of the RCT. The goal will be to maintain sertraline at the same acute dose that the participant was prescribed at the time of randomization to the RCT. Because participants will have been taking sertraline for a minimum of 10 weeks and a maximum of 20 weeks before entering the RCT, we anticipate that the dose of sertraline will rarely need to be adjusted in the RCT because of side effects. However, if for any reason, side effects do necessitate a dose reduction, the reason for contemplating a dose reduction will need to be discussed with the site’s principal investigator, to ensure that this is the most appropriate course of action. If a dose reduction is agreed upon, the dose can be reduced by 50 mg increments every 7 days, to a minimum dose of 50 mg/day, if required. An alternative approach to side effect burden during the RCT would be to disallow any reduction in the dose of sertraline, so as not to confound the analyses of relapse and recurrence. However, forcing a participant to leave the RCT because of intolerable side effects, when a dose reduction may alleviate the problem and allow the participant to continue, does not reflect ‘real world’ clinical practice, and would potentially weaken the power of the statistical models through forced attrition. An increase in dose of sertraline will not be permitted at any time during the RCT, because it will confound testing of H1. Dose changes of sertraline will be carefully recorded and will be reported in a descriptive fashion for each treatment arm.

A3.2 Placebo-Controlled Olanzapine Discontinuation: Eli Lilly has agreed to donate Olanzapine and matching placebo to the study. The placebo will be identical in size, weight, and appearance to the 5 mg olanzapine tablets that participants took during the acute and stabilization phases of the study. With the exception of Dr. Leon and research pharmacists at each study site, none of the study’s research personnel or study’s participants will be aware of treatment assignment. The following table lists the schedule for the substitution of ‘blinded’ olanzapine or placebo for open-label olanzapine, depending on the number of olanzapine pills the participant takes at the time of starting the switch.

Table: Schedule of Randomized, Double-Blind Switch of Open-Label Olanzapine to ‘Blinded’ Olanzapine Or Placebo

Switch Week	4 pills		3 pills		2 pills		1 pill	
	Bottle A	Bottle B	Bottle A	Bottle B	Bottle A	Bottle B	Bottle A	Bottle B
Week 1	3	1	2	1	1	1	1	0
Week 2	2	2	2	1	1	1	1	0
Week 3	1	3	1	2	1	1	1	0
Week 4	1	3	1	2	1	1	1	0
Thereafter	0	4	0	3	0	2	0	1

Bottle A = Open-Label Olanzapine; Bottle B = ‘Blinded’ Olanzapine or Placebo

A3.3 Dose Adjustments of Olanzapine/Placebo During the RCT: The goal will be to maintain olanzapine/placebo at the same acute dose that the participant was prescribed at the time of randomization to the RCT. However, a change in dose of olanzapine/placebo will be permitted, if necessitated by adverse effects or clinical worsening during the RCT. The rationale for allowing a change in olanzapine/placebo dose, is that the primary aim of the study is to assess whether olanzapine, administered within a clinically relevant dose range, prevents relapse, not whether a specific dose of olanzapine prevents relapse. Moreover, permitting a dose adjustment in response to side effects or symptoms of the illness reflects ‘real world’ practice and increases the likelihood of retention of participants in the study. If a change in dose of olanzapine/placebo is indicated, the daily dose can be adjusted by 1 tablet every 7 days, as needed, within the dose range of 5-20 mg/day of olanzapine/placebo. The reason(s) for each change of dose will need to be discussed with the site’s PI and will be documented in the case record form. Dose changes of olanzapine/placebo will be carefully recorded and will be reported in a descriptive fashion for each treatment arm.

A3.4 Lorazepam and Benzotropine During the RCT: If lorazepam is prescribed during the acute phase of treatment, an attempt will be made to taper and discontinue this medication during the acute phase, once patients experience improvement in depressive symptoms. However, if necessary, lorazepam may be

continued during the RCT, up to a maximum dose of 3 mg/day, for treatment of residual insomnia or anxiety. If benzotropine is required during the acute phase of treatment, it may be continued during the RCT, up to a maximum of 2 mg/day. [In STOP-PD, only 5/259 (1.9%) participants required benzotropine, so we anticipate very few patients will need this medication during the RCT].

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