COVER PAGE

Study Title:

The Role of Antidepressants or Antipsychotics in Preventing Psychosis: Fluoxetine vs Aripiprazole Comparative Trial (FACT)

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The Role of Antidepressants or Antipsychotics in Preventing Psychosis: Fluoxetine vs Aripiprazole Comparative Trial (FACT)

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Specific Aims

The early identification and prevention of schizophrenia has become a vital clinical and research goal. Research conducted over the past ten years, including work from our ACISR, has been instrumental in the development of effective criteria for the identification of young people at heightened risk for psychosis. Moreover, early data suggest that administration of antipsychotic drugs during the prepsychotic or "prodromal" illness phase (characterized by emerging attenuated positive symptoms) may reduce prepsychotic symptoms, improve functioning and reduce progression to full blown psychosis (Correll et al. 2010).

In other areas of medicine, however, treatments for the prevention or amelioration of early illness expression may differ from those utilized in the full-blown disorder. Therefore, we conducted an open label, non-randomized pilot study in which we compared treatment response to the class of antidepressants versus antipsychotic drug treatment on treatment response in 48 adolescents considered to be at high risk for schizophrenia. Our data (Cornblatt et al. 2007) suggested that the antidepressants, initiated naturalistically by treating physicians, were associated with less conversion to psychosis as compared with second-generation antipsychotic drug treatment. Of importance for our hypotheses, it appeared that that the advantage of antidepressants in preventing transition to psychosis was mediated by a significantly higher rate of non-adherence associated with antipsychotic drug treatment. Moreover, relevant to the well-being of patients, adverse effect potentials between antidepressants and antipsychotics differ in youth, favoring antidepressants (Correll et al. 2011).

While these first findings of a protective effect of antidepressants in prodromal individuals add to an intriguing line of primarily indirect evidence suggesting that antidepressants, which have a favorable risk-benefit ratio, may influence the development of psychosis, the lack of randomization and potential of prescriber bias reduce the interpretability of these early data. Therefore, we now propose to conduct a randomized, controlled 6-month pilot study comparing the antidepressant fluoxetine with the second generation antipsychotic aripiprazole in 48 subjects aged 12-25 years with at least moderate attenuated positive symptoms that developed within the past five years. Since transition to psychosis can occur at a relatively low rate over a very variable and potentially long time frame, and since discontinuation rates in long-term studies of putatively prodromal cohorts have been very high, we have designed a randomized, double-blind study focusing on intermediate outcomes, including the composite of all-cause-discontinuation and/or addition of a major psychotropic medication (see below), symptom change, safety, and adherence. The specific aims are:

Specific Primary Aim 1: To compare fluoxetine and aripiprazole on the likelihood of and time to all-cause discontinuation/need to add another psychiatric medication, symptomatic improvement, and adverse effects

Primary Hypothesis 1: Compared to aripiprazole, significantly fewer patients on fluoxetine will either discontinue treatment or require the addition of an antipsychotic, mood stabilizer, antidepressant or of >3 weeks of treatment with an anxiolytic/hypnotic

Secondary Hypothesis 1: Compared to aripiprazole, time to all-cause discontinuation or need to add another psychiatric medication (as defined above) will be significantly longer with fluoxetine

Secondary Hypothesis 2: Compared to aripiprazole, changes in attenuated positive, negative and general psychopathology will be similar with fluoxetine.

Secondary Hypothesis 3: Compared to aripiprazole, fluoxetine will be associated with significantly lower rates of adverse effects.

Specific Secondary Aim 1: To compare the effect of fluoxetine and aripiprazole on social and role functioning and subjective well-being in individuals at risk for schizophrenia.

Primary Hypothesis 1: Compared to aripiprazole, fluoxetine will lead to significantly greater improvement in social and role functioning.

Secondary Hypothesis 1: Compared to aripiprazole, fluoxetine will lead to greater subjective well-being.

Exploratory Aim: To compare the effect of fluoxetine and aripiprazole on peripherally measured levels of brain derived neurotrophic factor (BDNF).

Exploratory Hypothesis 1: Compared to aripiprazole, fluoxetine will lead to significantly greater increases in BDNF.

Background and Significance

Early Recognition and Prevention During the Psychotic Prodrome. After more than five decades of increasingly refined psychopharmacologic developments, schizophrenia has remained one of the most severe and disabling disorders in medicine. Since interventions after a first schizophrenia episode have not been able to alter the generally chronic and relapsing disease course (Robinson et al. 2004), early intervention and prevention of schizophrenia are a vital goal. Initial, retrospective studies that demonstrated presence of a symptomatic prepsychotic illness phase of clinically relevant severity and duration (Hafner et al. 1999) provided the practical basis for early identification efforts. Several lines of evidence further supported the potential utility of early interventions for the schizophrenia prodrome. These include an increasing appreciation that schizophrenia is a neurodevelopmental disorder characterized by early developmental delays and problems, and that is further associated with a significant functional decline and brain morphological changes (Correll and Kane 2004; Sawa and Snyder, 2002; Woods, 1998). Moreover, the duration of untreated psychosis (Marshall et al. 2005), and number of relapses have been associated with decreased grey matter and worse functional outcomes, even after controlling for potentially relevant confounders (Perkins et al. 2005). Importantly, brain morphological changes have also been demonstrated during the transition from prodromal psychosis to full blown psychosis (Pantelis et al. 2003), suggesting that early intervention may be a potential vehicle to effectively interrupt biological processes involved in the development of psychosis and its adverse functional consequences (Correll et al. 2010).

Prodromal schizophrenia research conducted over the past ten years at our Center and others has further consolidated the evidence that early identification and intervention studies during the schizophrenia prodrome are possible (Correll et al. 2010). Early recognition programs have identified high risk samples with conversion rates to psychosis between 10 and 40% over one to two years (Yung et al. 2008). In the largest study to date by the North American Prodromal Longitudinal Study (NAPLS) group of which Dr. Cornblatt at our Center is one of the PIs, a conversion rate of 35.3% over 2.5 years was reported (Cannon et al. 2008). These conversion rates to psychosis are 10-40 times the prevalence rate observed in the general population and far greater than the expected incidence rate during such a brief time period (Eaton 1999).

Evidence for the Potential Utility of Antipsychotics for the Prevention of Psychosis. Three randomized controlled intervention trials have been completed that included antipsychotics as the active treatment. These studies show that 6 months of treatment with low dose risperidone + CBT (McGorry et al. 2002) and 12 months of treatment with low dose amisulpride (Ruhrmann et al. 2007 and unpublished data) were associated with a significantly reduced transition to suprathreshold psychosis compared to needs based interventions that did not include antipsychotic drug treatment. The third trial showed a trend toward significance (p=0.08) comparing 12 months of olanzapine treatment with placebo, allowing psychotherapy in both groups (McGlashan et al. 2006). However, both at 8 weeks (Woods et al. 2003) and 12 months (McGlashan et al. 2006) several symptom ratings improved significantly more in the olanzapine treated group. Non-adherence rates were high and group differences diminished during longer term follow-up off all interventions, primarily due to a relative increase in conversions to psychosis in the patients initially randomized to active treatment.

Evidence for the Potential Utility of Antidepressants for the Prevention of Psychosis. Several lines of research - including epidemiologic, pharmacologic and clinical trials evidence - suggest that antidepressants may have a role in preventing psychotic disorders and psychotic relapses. Retrospective (Hafner et al. 1999; Hafner et al. 2005) and prospective studies (Correll et al. 2005) have shown that depressive symptoms are an integral part of the psychotic prodrome, preceding the onset of attenuated positive symptoms by approximately five years (Hafner et al. 1999). Furthermore, antidepressants are increasingly recognized to have neuroprotective properties (Li et al. 2000; Malberg 2000; Sanchez et al. 2001; Salzman et al.1994), increasing levels of brain derived neurotrophic factor (Rantamaki et al. 2007 De Foubert et al. 2004; Calabrese et al. 2007), which has been found to be low in post-mortem studies of patient with schizophrenia (Hashimoto et al. 2005; Weickert et al. 2005) in plasma (Toyooka et al. 2002; Huang and Lee, 2006; Pirildar et al. 2004; Buckley et al. 2007) and in CSF (Pillai et al. 2008) of schizophrenia patients compared to controls. Finally, two naturalistic studies in

individuals considered at high risk for the development of schizophrenia suggested that antidepressants might reduce conversion to psychosis (Cornblatt et al. 2007; Fusar-Poli et al. 2007), longer duration of antidepressant treatment was associated with full recovery of any syndromal or subthreshold positive or negative symptoms in patients with psychosis NOS (Correll et al. 2008), schizophrenia patients with postpsychotic depression randomized to imipramine were significantly less likely to relapse into depression as well as psychosis (0% vs. 50%, $p<0.02$) than patients randomized to placebo (Siris et al 1994). Furthermore, a recent meta-analysis of five small scale (n's=25-30), randomized, placebo-controlled studies in patients with predominantly negative symptoms found a significant advantage of antidepressant treatment compared to placebo for the reduction of negative symptoms (Rummel et al. 2005). These data have attracted significant interest in the research and clinical community because the availability of a non-antipsychotic, low-risk intervention for the psychotic prodrome would enhance patient care, have profound implications for research on the pathophysiology of psychosis, and could provide leads for future drug development strategies.

Potetntial Moderators of Psychosis Risk
There is converging evidence that neuroinflammation (Miller et al. 2011), oxidative stress (Flatow et al. 2013) and low levels of neurogenesis promoting factors, such as brain derived neurotrophic factor (BDNF) (Buckley et al. 2011) are involved in schizophrenia. These findings are of considerable interest in the context of the proposed study, as certain antidepressants seem to reduce markers of inflammation and oxidative stress on the one hand, and increase BDNF, on the other. In a meta-analysis of 20 studies, including 1,504 patients, the effect size for increasing peripherally measured BDNF levels was 0.62 (95% CI=0.36-0.88), which is considered a moderate effect and suggests that BDNF-mediated neurogenesis might be a critical factor involved in antidepressant efficacy (Brunoni et al. 2008).

Preliminary Data
In our open, naturalistic study of 48 patients (mean age: 15.8 years) followed for at least 6 months (mean: 30.5 months), we observed significantly lower transition to psychosis in the group treated with antidepressants (0%) compared to those receiving antipsychotics (43%) ($p<.007$) (Cornblatt et al. 2007). However, we were cautious in the interpretation of these data because 10/11 conversions in the antipsychotic-treated group occurred after the antipsychotic agent had been discontinued, (mostly longer than 6 months prior to the full manifestation of psychosis) and adherence rates were significantly higher in the antidepressant treated group(61% vs 21%, $p=.005$). While improvement in positive symptoms was significant ($p<.001$) and similar in both treatment groups, disorganized symptoms did not improve with either treatment. The non-random treatment assignment in this study calls for a randomized controlled study to follow up on these intriguing results.

Research Plan
Study design. We will conduct a Randomized, 24-week, double-blind study, comparing fluoxetine with aripiprazole in 48 patients with attenuated positive symptoms at a level of at least moderate severity. In choosing the antidepressant and the antipsychotic medication for this trial, we sought medications that had strong available evidence for their efficacy and safety, a high benefit-to-risk ratio, current FDA approval for use in adolescents who will be a core patient group for this study, and a longer half life in order to minimize treatment gaps when doses are taken irregularly. Moreover, since patients in this study will not have suprathreshold psychotic symptoms, choosing an antipsychotic with the least short- and long-term safety concerns was important to increase patient and family acceptability and to be in equipoise about these two intervention strategies. Based on these criteria, we chose fluoxetine over other antidepressant alternatives and aripiprazole over other antipsychotic alternatives.

Inclusion Criteria: 1) consent obtained from patients and their parents (assent for patients under 18); 2) age 12-25 years (inclusive); 3) English-speaking; 4) at least one positive (Scale A) SOPS score of 3-5, i.e., moderate, moderately severe or severe.

Exclusion Criteria: 1) lifetime diagnosis of an Axis I psychotic disorder, including: schizophreniform disorder, schizophrenia, schizoaffective disorder, bipolar disorder, or major depression with psychotic features; 2) current psychosis (any positive symptom SOPS score of 6, i.e., extreme); 3) current diagnosis of Major Depressive Disorder, single episode or recurrent, severe without psychotic features; 4) current stimulant treatment; 5) history of neurological, neuroendocrine or other medical condition known to affect the brain; 6)

any significant medical condition that contra-indicates treatment with either aripiprazole or fluoxetine; 7) past or current substance dependence; sunstance abuse within the last 4 weeks; 8) IQ < 70.

Recruitment. We will recruit patients utilizing the ACISR Trials Operation Unit, which has developed recruitment strategies within the child and adolescent as well as adult outpatient and emergency room services at Zucker Hillside Hospital, with additional referrals from the inpatient units. In addition, to increase the pool of potentially eligible patients, our ACISR maintains a Research Network that will liaise with local community mental health clinics offering a screening program for potentially prodromal symptoms in the clinic clientele. We will approach mental health clinics associated with Queens Child Guidance Center (5 clinics), North Shore Child Guidance Center (3 clinics), South Shore Child Guidance Center , Penninsula Counseling Center, Pederson-Krag Center, as well as the outpatient clinics of Kings County Hospital and Stony Brook Hospital. Finally, we are setting up a collaboration with the St Luke's Roosevelt hospital PEER program in Manhattan, a dedicated first episode and prodromal psychosis outpatient program that just received 2-year structural funding from the van Ammeringen Foundation. Furthermore, we are in contact with the psychiatry department at SUNY Downstate. St. Luke's Roosevelt and, potentially SYNU Downstate, will become sites for this study and will need to obtain their own IRB approval. The other mental health clinics will be utilized as referral sources. Thus, while presentations and outreach will take place, patients will not be assessed and treated at these centers; treatment will reside at the treatment sites, namely Zucker Hillside Hospital, St. Luke's Medical Center and, possibly SUNY Downstate.

Medication Schedule. Randomization codes to either aripiprazole or fluoxetine will be provided by the NSLIJ biostatistics group. To increase homogeneity and assure treatment with a clinically effective dose, patients will undergo a fixed titration phase during the first three weeks, with the option to slow or halt the titration or

Table 1.	Wk 0/Wk 1	Wk 1/2	Wk 2/3	Week 4-Week 24
Titration	Fixed	Fixed	Fixed	Flexible Dosing, Range
Fluoxetine	10 mg	10 mg	20 mg	10mg – 60mg
Aripiprazole	2 mg	5 mg	10 mg	5mg – 30mg

decrease the target dose if intolerability develops (Table 1). After 3 weeks, dosing will be flexible and left up to clinical choice and need.

Adjunctive Therapies. Based on our previous experience with administration of fluoxetine and aripiprazole in prodromal patients, we expect the need for rescue medication to be relatively infrequent. However, adjunctive medication will be available to address clinically relevant, treatment emergent side effects. These include: benztropine (up to 2 mg bid) for extrapyramidal symptoms (EPS) in case dose reduction is ineffective or undesired; lorazepam (up to 1 mg bid) to treat restlessness, anxiety or agitation, or to improve sleep; and propranolol (up to 20 mg tid) for akathisia. Moreover, when a patient develops ≥7% weight gain, which triggers healthy lifestyle interventions involving simple education regarding diet and physical activity, and despite this exceeds 10% weight gain, metformimn (500-2000 mg) will be offered. After the patient is symptom free for at least two weeks a slow withdrawal of the adjunctive medication will be attempted. Patients will also receive supportive psychotherapy by during regular medication visits. Needs based individual psychotherapy will be provided for crisis situations and in a time limited fashion (i.e., six sessions).

Assessments. Table 2 summarizes the proposed diagnostic, efficacy and safety assessments throughout the 24-week study. Subjects can still be assessed +/- 7 days of their propsed assessment date in the event that there are unable to come in at the proposed time.

The ACISR Trials Operation Unit maintains a cadre of trained raters and assessors with experience in the majority of measures utilized, the Clinical Assessment Strategies Unit has been instrumental in the development of individual assessment measures of patient function, and the Adverse Event Unit provides expertise in the assessment and management of drug-induced adverse events, of particular importance in this population who may be more sensitive to drug side effects, and which may predict non-adherence.

Patients who discontinue the assigned medication or who initiate treatment with a medication that is not allowed as per the protocol will have an unscheduled study termination visit, but patients will be assessed at

the predetermined time points independent of whether they are compliant with the study protocol to allow for an ITT analysis. The primary outcome variable for this project will be discontinuation of medication or addition, as verified by prescription, of another psychotropic medication to the daily treatment regimen of the subject (excluding prn medications). Patients that are not compliant at least 80% of the time will be subject to an unscheduled study termination.

Optional Genetic Test Component

Once during the study period, each subject will be asked to provide an additional 16 ml blood sample (approximately 1 tablespoon) for DNA collection and genotyping. The collected blood samples will be stored in locked freezers. Blood samples will be transferred to the Feinstein Institute for Medical Research (Dr. Gregersen's lab) Human Genetics Program core facility for lymphocyte extraction. From this lymphocyte extraction, 50% will be used for direct DNA extraction and 50% will be utilized to establish Epstein-Barr virus-transformed cell lines. We will store the DNA for future exploratory analyses comparing patients with conversion to psychosis or worsening of prepsychotic symptomatology to those patients who did not worsen or convert. These exploratory analyses will target potentionally relevant genomic regions involved in schizophrenia and genomic regions involved in conversion to psychosis potentially identified by then in other prodromal research cohorts.

Analytic Plan

General Considerations. All analyses will be conducted in an ITT sample using all randomized patients who received at least one dose of medication. Although the analytic methods to be described below (i.e. survival analysis, mixed models, RMANOVA, etc.) are fairly routine, missing data can cause problems in the statistical analyses. Thus, if the necessary, we will consider the use of multiple imputation techniques (i.e., PROC MI and PROC MIANALYZE), using the assumption of data being "missing at random" (MAR). In this case, we will transform non-monotone missing data patterns to monotone patterns, which are easier to analyze.

Specific Primary Aim 1. To compare fluoxetine and aripiprazole on time to all-cause-discontinuation/need to add another psychotropic agent, prodromal symptom change and adverse effects in prodromal individuals. Binary outcomes, such as the primary composite outcome variable and the dichotomized presence of specific side effects (i.e., present=moderate severity or higher) or non-adherence, will be analyzed using chi squared test or Fischer's Exact test, as necessary. Standard methods of survival analysis (Kaplan-Meier product-limit method, logrank test, Cox proportional hazards regression) will be applied to the secondary, time dependent variable "time until all-cause-discontinuation/need to add another psychotropic". If during the trial a subject is lost to follow up, that subject's data will be "censored" at the week of dropout. Cox proportional hazards regression model will be used to determine which factors (if any) are predictive of all cause discontinuation. In addition to the ITT analyses, we will also conduct a sensitivity analysis using only data from subjects as long as they remained on the assigned treatment, censoring data at the week of treatment discontinuation.
Repeated measures analysis of variance (RMANOVA) using a mixed models approach (SAS PROC MIXED, SAS Institute, Cary, NC) will be used to examine the longitudinal and between-drug patterns in continuous outcomes, such as psychopathology rating scores and severity of side effects. In case of relevant missing data, PROC MIXED will be able to model the data despite the missing values. RMANOVA using the mixed models approach will be utilized to analyze changes in weight, BMI and HOMA-IR (using the log ratio transformation). The method of generalized estimating equations (GEE) will be used to analyze ordinal data, such as Barnes and Simpson-Angus scores.

Specific Secondary Aim. To compare the effect of fluoxetine and aripiprazole on social and role functioning and subjective well-being in individuals at risk for schizophrenia. As for primary aim 1, repeated measures analysis of variance (RMANOVA) using a mixed models approach (SAS PROC MIXED, SAS Institute, Cary, NC) will be used to examine the longitudinal and between-drug patterns in these continuous outcomes. In addition, the correlation between social and role functioning scale score changes and changes in attenuated positive and negative symptoms scores will be analyzed using the Bland and Altman methodology. Likewise, correlations between changes in subjective well being and psychopathology scores as well as side effect change scores will be analyzed using that same methodology.

Table 2: Assessment Timetable

Weeks/ Months	Pre-screen	Screen	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24
Assessments													
MD													
Physical Examination		+											
SAFTEE (side effects)			+	+	+	+	+	+	+	+	+	+	+
Psychometrician													
Kid-SCID		+											
Premorbid Adjustment		+											
IQ Test		+											
SIPS/SOPS	+	+	+	+	+	+	+	+	+	+	+	+	+
BPRS, SANSS			+	+	+	+	+	+	+	+	+	+	+
CGI			+	+	+	+	+	+	+	+	+	+	+
Hamilton Scale for Depression			+	+	+	+	+	+	+	+	+	+	+
Young Mania Rating Scale			+	+	+	+	+	+	+	+	+	+	+
Drug Attitude Inventory			+				+		+	+	+		+
Social Functioning and Role Functioning Scale			+							+			+
Subjective Wellbeing Scale (SWN-K, Naber 1995)			+							+			+
Research Technician													
Simpson-Angus (EPS)			+	+	+	+	+	+	+	+	+	+	+
Barnes Akathisia			+	+	+	+	+	+	+	+	+	+	+
AIMS (Dyskinesia)			+	+	+	+	+	+	+	+	+	+	+
Vital signs/Weight			+	+	+	+	+	+	+	+	+	+	+
Fasting blood tests (CBC, comprehensive metabolic panel, glucose, insulin, lipid profile, TSH, LFTs) and urine analysis		+ [a]	+				+		+	+			+
Study medication level							+		+	+			+
Pregnancy test (urine[d] or serum)		+	+				+		+	+			+
Urine toxicology		+	+				+		+	+			+
DNA blood draw & storage (optional)			+[b]										
Brain Derived Neurotrophic Factor		+	+				+		+	+			+

[a] can be non-fasting, no insulin and lipid level required; [b] can be obtained at any time during the study if needed; [c] SIPS can be used from Pre-screen if screening done within 2 days.
[d] when subject outpatient, urine test will be used, when inpatient then we will use serum pregnancy test already for in unit.

Exploratory Aim. To compare the effect of fluoxetine and aripiprazole on BDNF levels to determine potentially beneficial neurotrophic effects that mediate symptomatic and/or functional benefits. Similar statistical methods as for the continuous outcomes in aim 1 and aim2 will be used.

Power Calculations and Sample Size. This is a pilot study with the aim to assess the feasibility of this design for a larger trial and to obtain preliminary data that would guide future power and effect size analyses. For the purposes of this trial, we used an estimate of a 40% difference between the two treatments on the combined primary outcome of all-cause-discontinuation and need for addition of another major psychiatric medication. Based on preliminary data, we estimated the rates to be 65% with antipsychotics and 25% with antidepressants. With 24 subjects in each treatment arm, we will have 82% power to find a statistical difference in the primary composite outcome in a two tailed t-tests with alpha <.05 (online calculator used for this power/sample size calculation: http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html). This is a conservative estimate, as repeated

measures ANOVA will yield greater power, compensating for any drop outs prior to the first post-baseline assessment.

HUMAN SUBJECTS
This human subjects research meets the definition for clinical research.

Protection of Human Subjects

1. Risks to the Subjects

Fluoxetine is approved by the Food and Drug Administration (FDA) for the treatment of depression, obsessive-compulsive disorder (OCD), and panic disorder in adults and for depression, anxiety and OCD in children and adolescents. Aripiprazole is approved by the FDA for the treatment of schizophrenia and bipolar didorder in adults and in children and adolescents age 10-17 (bipolar disorder) and age 13-17 (schizophrenia). Neither medication is specifically indicated in adolescents for the symptoms for which they are prescribed in this trial. However, both medications are widely used for a range of disorders in children and adolescents, and both have been used successfully in the RAP Program. This study includes detailed procedures for safety monitoring.

These procedures are outlined below.

There are a number of common, non-serious side effects associated with use of fluoxetine: nausea, diarrhea, intestinal discomfort, headache, insomnia, sexual side effects, dry mouth, fatigue/drowsiness and dizziness.

Recently, the Food and Drug Administration (FDA) issued a public health advisory concerning a possible link between worsening depression and emergence of suicidal ideation or behavior in patients treated with certain antidepressant medications, including but not limited to sertraline. The FDA has not concluded that these drugs cause worsening depression or suicidality: worsening of symptoms could be due to the underlying problem or might be a result of drug therapy. As a result, we will carefully monitor patients in this trial for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose either increases or decreases.

We will ask study participants to let us know immediately if they feel worse in any way, at any time during treatment. If suicidal thoughts begin or worsen, associated with taking medication, they will be urged to call the study doctor immediately. It is very important that participants do not abruptly stop taking the medication without first discussing this with the study doctor as suddenly stopping these medications may be followed by withdrawal symptoms or by a return of the depressive feelings.

Common, non-serious side effects for aripiprazole are extra-pyramidal symptoms (including tremor, stiffness, and restlessness), sedation, dizziness, either weight loss or weight gain, hyperglycemia (high blood sugar), nausea, dry mouth, headache and sexual side effects.

Two potentially serious but infrequent side effects have been associated with aripiprazole:

Tardive dyskinesia (TD), which includes abnormal movements of the mouth, face, tongue, arms or legs. For some people, the movements continue even if the medication is stopped. The extent to which risperidone causes TD has not yet been determined, but there is evidence that it is as low as 1% per year of treatment. This rate is as low as or lower than the TD rates for other FDA-approved medications in the same class.

Neuroleptic malignant syndrome (NMS), a very rare, but potentially serious disorder characterized by neurological changes, fever and other symptoms, has been reported with risperidone. If NMS develops, it typically does so shortly after medication is started. NMS is easily treatable and is readily detected by clinical evaluation that includes vital signs, the testing of muscle tone and blood tests if indicated. These evaluations will be performed at each psychiatric visit.

2. Adequacy of Protection Against Risks

a. Recruitment and informed consent

For each potentially eligible patient, a parent (or guardian) will be contacted by the treating physician to obtain permission to be contacted for participation in a research study. Following this permission, the treating physician, Co-I, or clinical psychologist affiliated with the study will discuss the study with the caregiver and the patient. Each parent will receive a complete explanation of the purposes, duration, procedures, and potential risks and benefits of this study. A similar explanation will be given to the child, commensurate with his/her age and ability to comprehend. Any questions that the family may have will be answered. If the family agrees to participate, written informed consent will be obtained from the parents and written assent from the child. A copy of the signed consent form will be placed in the child's medical record. Parents will be informed that both aripiprazole and fluoxetine are currently marketed medications, which can be prescribed by their physician for their child without study participation. The right of the family to withdraw the child from the study at any time will be made clear. Typically, several meetings with patients and family members will be devoted to the consent process. Because the study involves pharmacological interventions, a child and adolescent psychiatrist will always be involved in obtaining consent.

b. Protection against risk

The proposed medications are not experimental agents, but are being used widely in children and adolescents in general clinical practice. Participation in the proposed study will mean that patients will undergo regular, frequent careful assessments of adverse effect and of efficacy as outlined in table 2. This is a more rigorous assessment of risks and benefits than usually provided as part of general psychiatric community care. Moreover, the study will use predefined exit rules, such as a CGI-I score of much or very much worse or a 20% worsening on the BPRS scale, further protecting against risk from not benefiting from study participation.

To screen for and guard against suicidal ideation and suicidal behavior, the suicidality item in the HAM-D will be used as a screening tool. If any symptoms are rated greater than zero, this will be followed by a formal assessment with the Columbia-Suicide Severity Rating Scale (Mundt et al. 2010), and appropriate clinical steps will be initiated as needed. Additionally, for patients in whom weight gain of ≥7% is detected throughout the trial, healthy lifestyle interventions involving simple education regarding diet and physical activity will be implemented. If weight gain continues and exceeds 10% over baseline body weight, the subject may be withdrawn from the study or metformin can be offered as per clinical need while continuing in the study.

3. Potential of Benefits of the Proposed Research to the Subjects and Others

The patients who will be selected for inclusion in this study will be adolescents and young adults with symptoms and signs that fulfill criteria for the psychosis prodrome. No benefit can be promised to the study participant, him/herself, although the medication treatment in each arm can be expected to alleviate oftern imparing and/or distressing symptoms and signs consistent with a psychosis prodrome. Moreover, patienrts will benefit from close observation during the study. The blind for each study subject will be broken after all study data has been collected for that individual. The information about the response of the subject may be helpful for treatment planning.

4. Participant Compensation

Participants will be paid $30 for each of the 6 longer visits, ie, at screening and weeks 0, 4, 8, 12 and 24 ($180), and $20 for each of the 6 short visits at weeks, 1, 2, 3, 6, 16, and 20 ($120). Thus, total maximum compensation for complete participation in all 12 visits of this randomized controlled study will be $300 per participating family. If a participant withdraws before the study is completed, they will be paid for their participation up to that time. Compensation will be provided as check or cash after each reimbursable study visit with instructions that it is intended to support the entire family's expenses associated with the assessment. In addition, parking or public transportation costs will be reimbursed or transportation may be provided. Light, healthy meals or meal vouchers will be provided after fasting labs are obtained.

5. Importance of the Knowledge to be Gained

There are very few data to guide clinicians treating in young people with symptoms and signs that are consistent with the schizophrenia prodrome. It is critical that the efficacy and safety of non-antipsychotic drugs be studied specifically in this vulnerable patient population to improve the risk benefit ratio of available and commonly used second-generation antipsychotics in the treatment of the schizophrenia prodrome, both in clinical practice and in research settings.

6. Data Safety Monitoring Plan

The Data Safety Monitoring Board (DSMB) for this study will be affiliated with our ACISR (through which this study is funded). The DSMB will have access to all relevant clinical data necessary to assess the adequacy of human subjects protections provided throughout the study. Serious Adverse Events will be reported to DSMB members at the same time that they are reported to each IRB. In addition, summary reports of dropouts, adverse events, and other important events will be provided to the Board prior to their conference calls, which will occur twice yearly.

Handling of Serious Adverse Events

Bristol Myers Squibb will receive SAE reports immediately at the address below:

Bristol-Myers Squibb Company
Global Pharmacovigilance
Email: WorldWide.Safety@bms.com

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event.

  Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs.

Inclusion of Women

The study population will include representation of both genders and gender will not play a role in patient recruitment. Based on data collected in our open label study (Cornblatt et al. 2007), we expect approximately 40% of the sample to consist of females and 60% of the sample to consist of males (see target enrollment table). If we find that the patient female/male recruitment ration is significantly unbalanced, we will make special efforts to target a gender-specific population.

Inclusion of Minorities

Based on the results of our open label study (Cornblatt et al. 2007), we expect approximately 12% of patients to be of Hispanic or Latino ethnicity and 88% to be of ethnicities other than Hispanic or Latino. We also expect

approximately 6% of the patient sample will be Asian, 15% African-American, and 79% Caucasian. If we find that the patient sample is not representative of the patient population that we are recruiting from in terms of race or ethnicity we will make special efforts to target the under-represented groups.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: The Role of Antidepressant in the Schizophrenia Prodrome

Total Planned Enrollment: 48

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	3	5
Not Hispanic or Latino	115	24	35
Ethnic Category: Total of All Subjects *	17	27	48
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	5	7
White	14	21	35
Racial Categories: Total of All Subjects *	17	27	48

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

Inclusion of Children

This study focuses on children ages 12 to 17, as well as on adults ages 18-25. Since minor subjects will be involved in this study, the following procedures have been put into place to ensure their safety. All subjects will require written informed consent of a guardian in order to participate in the study, and will likewise be required to provide written informed assent for study participation, unless they are decisionally impaired, in which case minor assent will not be required.

Vertebrate Animals – N/A

Select Agent Research --N/A

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