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Efficacy and Tolerability of Olanzapine, Quetiapine and Risperidone in the Treatment of First Episode Psychosis: A Randomized Double Blind 52-Week Comparison

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Jeffrey A. Lieberman, MD
Diana O. Perkins, MD, MPH
Joseph McEvoy, MD
Hongbin Gu PhD
Robert Hamer PhD
Gary Koch PhD

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1. Background and Rationale

Schizophrenia is a serious, often disabling and recurrent mental illness. Previously, the prognosis of patients with schizophrenia was thought to be poor and the disease associated with an inexorably progressive course (McGlashan, 1988). However, studies of first episode patients early in their course of illness have demonstrated their superior treatment response (in comparison to chronic multi-episode patients) and ability to achieve symptomatic remission and good outcomes with the proper treatment (Lieberman et al., 1993; Robinson et al., 1999). In general first episode patients show enhanced sensitivity to both the therapeutic and side effects of treatment.

The advent of a new generation of "atypical" antipsychotics, including olanzapine, quetiapine and risperidone, has improved the potential for decreasing the morbidity and disability associated with schizophrenia. While the atypical antipsychotics have certain pharmacological properties in common (notably 5HT2A/C and D2 antagonism), there are important pharmacological differences with potential relevance for both safety and efficacy (Kinon & Lieberman, 1996). There are 17 published clinical trials comparing atypical with typical antipsychotics primarily in patients with chronic schizophrenia or schizoaffective disorder. These studies have predominantly included patients with longstanding and chronic illness, and generally report improved tolerability and comparable or improved efficacy of atypical over typical medications (Arvanitis & Miller, 1997; Beasley et al., 1997; Peuskens & Link, 1997; Small et al., 1997; Tollefson et al., 1997; Beasley Tollefson, et al., 1996; Beasley, Sanger, et al., 1996; Blin, Azorin & Bouhours, 1996; Borison, Arvanitis & Miller, 1996; Fabre et al., 1995; Peuskens, 1995; Marder & Meibach, 1994; Ceskova & Svestka, 1993; Chouinard et al., 1993; Hoyberg et al., 1993; Min et al., 1993; Claus et al., 1992). Little is known about the comparable efficacy and safety of the atypical antipsychotics, however, since few head to head double-blind comparisons trials have been completed and only in chronic patients. One published study reports a double-blind comparison of olanzapine with risperidone in 339 patients with schizophrenia, finding that the two medications produced roughly comparable symptom reduction but a higher proportion of patients responded to olanzapine, and olanzapine caused fewer EPS and sexual side effects (Tran et. al., 1997). A second study of both drugs found them comparably effective (although risperidone showed slight superiority on some symptom dimensions) and no different on EPS rates (Conley and Mahmoud, 2001). In both studies olanzapine exhibited greater weight gain. An open label 4-month study comparing quetiapine with risperidone in 751 patients with psychosis found similar improvement in positive and negative symptoms, but significantly greater improvement in depressive symptoms in quetiapine versus risperidone treated patients (Borison, Arvanitis & Miller, 1997). In this study quetiapine was better tolerated as evidenced by decreased incidence of substantial EPS.

It has been proposed that atypical antipsychotic medication should be used preferentially in the treatment of first episode patients with psychotic disorders (Lieberman 1996). First episode patients are an important population and in many ways ideal subjects to study the comparative benefits and tolerability of the atypical antipsychotics. First episode patients are a highly treatment responsive group, and may be best able to realize the full benefits of a drug. In addition, first episode patients are sensitive to side effects, especially extrapyramidal and weight gain side effects (Sanger et al., 1999). Thus, differences in tolerability may be highlighted in this patient population. They require lower doses on average than more chronic patients do. In addition, they will not have had lengthy prior exposure to antipsychotic medication treatment, and thus prior treatment effects do not confound differences in tolerability and treatment responsivity. It may be that clinical benefits of atypical antipsychotics will best be demonstrated in this more homogeneous and pristine patient population. There are preliminary data that are consistent with this premise. A sub-analysis of a 1,996 subject olanzapine clinical trial data base, where a group of 83 first-episode patients were identified (Sanger et al., 1999), suggested that olanzapine treated patients showed significantly greater improvements in the Brief Psychiatric Rating Scale (BPRS) total and negative scores and in the Positive and Negative Syndrome Scale (PANSS) total and positive scores compared to the patients treated with haloperidol. In addition, a greater proportion of olanzapine treated patients (67%) compared with haloperidol treated patients (29%) were rated as "clinically improved" by the end of the short-term trials (>40% reduction in the BPRS). The olanzapine treated patients experienced significantly less EPS than haloperidol treated patients. In addition, there have been several studies (either recently completed or still in progress) that have examined the comparative efficacy of the atypical drugs olanzapine and risperidone with each other and with conventional antipsychotics in first episode patients. However, there has been no study initiated to examine the comparative effects of quetiapine to the other atypical drugs. There are several reasons to believe that quetiapine may be an effective drug for treating patients with first episode psychosis. First, quetiapine has the lowest EPS liability of any antipsychotic drug. First episode patients are extremely sensitive to these effects and have a very high incidence (>70% with conventional drug treatment). Second, first episode patients are highly susceptible to weight gain associated with atypical antipsychotic therapy. Weight gain is particularly problematic in first episode patients as they are bothered by the cosmetic aspects of weight increases, and since they are likely to be on medication for years to come, are vulnerable to the medical consequences of the weight gain. Third, first episode patients require lower doses of medication to achieve therapeutic responses. Consequently, the wider dose range of quetiapine and the fact that it is currently being used at doses on the lower half of the therapeutic range will not be as much of a disadvantage in treating first episode patients. All of these factors contribute to patients' potential adherence to treatment. The issue of treatment adherence is of critical importance in first episode

patients. Recent studies have shown that although these patients respond very well (achieving 1 year remission rates of >80%) the 1-year attrition rates are as high as 60%. A significant cause of nonadherence is side effects and tolerability of medications.

2. Specific Aims

2.1. Overview

The purpose of this study is to compare the effectiveness, tolerability, and efficacy of the atypical antipsychotic drugs olanzapine (2.5-20 mg/day), quetiapine (100-800 mg/day) and risperidone (0.5-4 mg/day) in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder experiencing their first psychotic episode. The study design is a randomized, double-blind, parallel and symmetrical 3-arm 52 week clinical trial.

2.2. Primary Aim

The primary aim of this trial is to evaluate the effectiveness of olanzapine, quetiapine, and risperidone in the treatment of the first episode of psychosis. The primary outcome variable to evaluate effectiveness is "all cause pharmacologic treatment discontinuation," as reflected by the proportion of patients that discontinue from the study prior to 52 weeks of treatment. This outcome measure was chosen due to its high clinical relevance and the fact that it integrates both tolerability and efficacy. The primary hypothesis is two-fold: that quetiapine is non-inferior to risperidone, and that quetiapine is non-inferior to olanzapine, in the rates of all cause pharmacologic treatment discontinuation.

2.3. Secondary Aims

The secondary aims of this trial are:

a) To evaluate the effectiveness of olanzapine, quetiapine, and risperidone in the treatment of the first episode of psychosis by comparing the time to "all-cause pharmacologic treatment discontinuation."

b) To examine the efficacy of olanzapine, quetiapine, and risperidone in treating symptoms of schizophrenia, as follows:

   1. Effects on total symptoms, and on positive, negative, mood, insight into illness (ITAQ) and substance use symptoms at 12, 24 and 52 weeks (or LOCF) of treatment, as measured by change from baseline in PANSS total score, positive and negative sub-scales, the Calgary Depression Rating Scale, and substance use (AUS/DUS).

   2. Effects on neurocognition (attention, memory, executive function, social cognition) at 12 and 52 weeks (or LOCF), as measured by change from baseline.

3. The proportion of individuals that are remitted (defined as no item on the PANSS > 3 and CGI rated "mildly ill" or less).
4. Time to illness remission.
5. Proportion of subjects that end study participation due to lack of efficacy prior to 52 weeks of treatment.
6. Quality of life (QOL) and service utilization outcomes at 12, 24 and 52 weeks (or LOCF).

c) To compare the tolerability of olanzapine, quetiapine, and risperidone in first episode patients as indicated by:

1. Risk of akathisia (Barnes global score >2), Parkinsonian symptoms (Simpson Angus total score > 3), and clinically significant EPS (indicated by treatment with benztropine, lorazepam or propranolol for treatment of medication side effects at any time prior to the evaluation time point) at 12, 24 and 52 weeks (or LOCF) of treatment.
2. Proportion of subjects that end study participation due to intolerance prior to 52 weeks of treatment.
3. Proportion of subjects that have a clinically significant increase in weight (increase in BMI of 3 or more points) and proportion of subjects that are obese (BMI > 30) at 12, 24, and 52 weeks of treatment.
4. Mean change in fasting cholesterol, triglycerides, HgA1c and glucose at 12, 24 and 52 weeks (or LOCF) of treatment.
5. Mean change in prolactin, estrogen or testosterone level and proportion of subjects with sexual adverse effects at 12 and 52 weeks (or LOCF) of treatment.
6. Change (baseline to highest value) of: akathisia (Barnes Akathisia Scale), Parkinsonism (Simpson-Angus Rating Scale), weight gain and frequency of adverse events at 12, 24 and 52 weeks (or LOCF) of treatment.
7. Overall adherence to treatment at 12, 24 and 52 weeks (or LOCF). Adherence is defined on a 4-point likert scale, rated after a structured clinical interview (please see Source Document for details, adherence is rated as: 1=always/almost always, 76-100% of the time; 2=Usually, 51-75% of the time; 3=Sometimes, 26-50% of the time; 4=Never/Almost never, 0-25% of the time).

Phase 2: V6-9	11-17 days	14 days
Phase 2: V10-19	25-31 days	28 days

Eliminated: Phase 3: V20-23

3.2.4. Enrollment

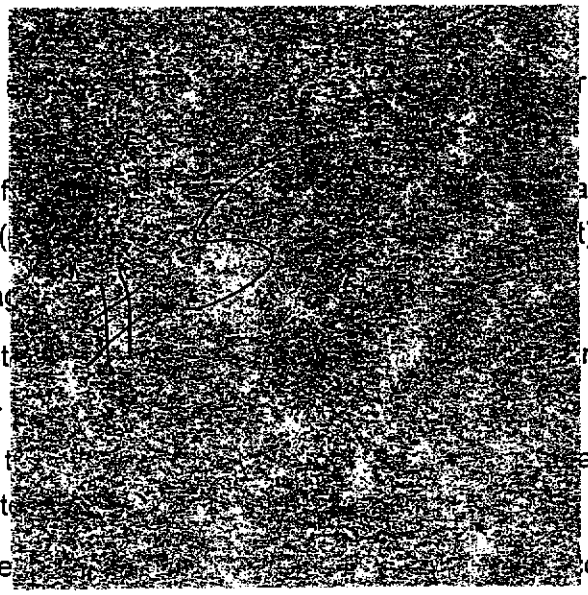
An informed consent document approved by an ethical review board or similar body will be signed by the patient or the patient's authorized legal representative prior to the patient's participation in this study.

3.3. Selection of Study Population

3.3.1. Study Selection Record

The study subjects will be recruited from patients who present to inpatient, outpatient, or emergency room services for the evaluation and treatment of psychosis. Study subjects may also be ascertained through media advertising, at the discretion of the site principal investigator with the approval of the sponsor (AstraZeneca) and the IRB.

3.3.2. Inclusion Criteria



1. Meets DSM IV criteria for schizoaffective disorder.
2. Has no previous history of an antipsychotic medication ().
3. Between 16-40 years of a
4. Psychotic symptoms must more than 5 years (60 months).
5. Able to fully participate in al guardian able to participat
6. Female patients of childbe cepted means of contraception.
7. Score on at least one PANSS psychosis items (P1, P2, P3, P5, or P6) $\geq$ 4 and CGI Severity score $\geq$4 (moderate) at point of maximum severity of illness to date.

3.3.3. Exclusion Criteria:

1. Past history of any DSM-IV psychotic disorder with recovery. Recovery is defined as a period of at least 3 months with no active positive symptoms.
2. Patients with heavy co-morbid substance use, where the presenting psychotic symptoms are judged by the study physician as likely to be substance induced.

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3. Female patients who are either pregnant or nursing.
4. Known history of mental retardation.
5. Non-english speaking (mastery of English insufficient to participate in study evaluation procedures).
6. Serious, unstable medical illness.
7. Known allergy to any study medication.
8. At serious suicidal risk.
9. Participation in clinical trial of an investigational drug within 30 days of visit 1.

3.3.4. Discontinuation of Subjects from Treatment or Assessment

3.3.4.1. Criteria for Discontinuation

Patients may be withdrawn from the trial for any of the following reasons:

1. Inadequate therapeutic effect (requiring alternative treatment). (Note: subjects shall not be withdrawn due to lack of efficacy if the maximum dose has not been achieved; except if the patient is not having adequate response but higher doses are not tolerated, then this can be considered as a discontinuation for lack of efficacy.)
2. Unacceptable side effects
3. Patient decision (examples include but are not limited to):
    a. Withdrawal of informed consent.
    b. Subject lost to follow-up (dropouts).
4. Administrative (examples include but are not limited to):
    a. Site protocol noncompliance (protocol violations or deviations).
    b. Other independent external events that preclude further participation in the protocol for a subject who would otherwise continue (e.g. moving, accidental death, pregnancy).

The reason for withdrawal must be documented on the CRF provided. If a subject is withdrawn due to an adverse event, then the adverse event must be specified on the CRF provided. If a subject is withdrawn all assessments that are specified for the end of the trial period should be carried out wherever possible. All withdrawals due to serious AEs must be reported to Quintiles' Safety Surveillance and Reporting office within 1 day. Withdrawals

due to the occurrence of non-serious AEs must be reported to Quintiles' Safety Surveillance and Reporting office within 15 days.

Any subject who withdraws during the trial and has clinically significant or abnormal findings on any safety assessment will have a follow-up visit within 1 week and at appropriate intervals thereafter until the abnormality resolves. Where possible, patients should be followed up for 30 days after the last dose of trial drug is given. All deaths and all serious AEs should be reported to Quintiles' Safety Surveillance and Reporting office. On-going AE's should be followed up until resolved or stabilized.

3.3.4.2. Voluntary Discontinuation by a Subject

Subjects are free to discontinue their participation in the study at any time, without prejudice to further treatment. Subjects who discontinue from the study should be asked about the reason(s) for their discontinuation and about the presence of any adverse events.. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up and the subject should return all investigational products.

3.4. Treatments

3.4.1. Investigational Products

The following drugs are used in this trial:

- Quetiapine (Seroquel) distributed by AstraZeneca, Inc., supplied by the sponsor in dosage of 100 mg.
- Risperidone distributed by Janssen Pharmaceutica Inc., purchased by the sponsor in dosage of 0.5 mg.
- Olanzapine distributed by Lilly Inc., purchased by the sponsor in dosage of 2.5 mg.

Capsule strengths are listed below:

Medication	Capsule Strength
Olanzapine	2.5 mg
Quetiapine	100 mg
Risperidone	0.5 mg

3.4.1.1. Drug Packaging & Labeling Design

Over-encapsulated study drug capsules will be filled into high-density polyethylene bottles, which will be capped using child resistant closures with induction inner seals. Each bottle will contain one-hundred twenty-four (124) capsules.

3.4.1.2. Storage and Inventory Management

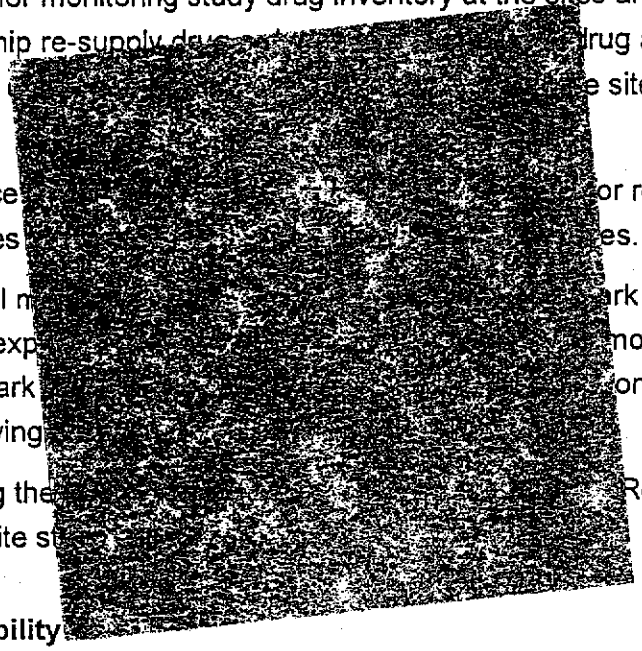
All product will be monitored in a secure, limited access area at controlled room temperature.

Quintiles will be responsible for monitoring study drug inventory at the sites and notifying the distribution center when to ship re-supply dru rug at the site falls below its re-order point, then e site up to its respective target level).

The Quintiles interactive voice or re-ordering study drug replacement boxes es.

The Quintiles IVR system will m rk drug as expired 60 days prior to the exp monitor drug expiration at the sites and mark on date to prevent a subject from receiving

Specific procedures for using the Reference Manual to be distributed at site s



3.4.1.3. Accountability

The investigator, his/her designee or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all trial supplies using the Drug Accountability Form. These forms must be available for inspection at any time. Trial drug prescription, dispensing and compliance will be captured on the case report forms and will be source validated by Quintiles monitors.

3.4.2. Doses and Treatment Regimens

3.4.2.1. Dosing and Administration

All subjects will begin with one capsule (olanzapine 2.5 mg, quetiapine 100 mg, risperidone .5 mg). During the first 6 weeks of treatment, medication may be increased by one capsule at the discretion of the clinician with a minimal period between dose increases of 48 hours. Dose increases should be made based on clinical response and tolerability, and it is recommended that the length of the dosing intervals be increased if the subject experiences medication side effects. The recommended initial target dose is 2 study pills BID (e.g. BID of olanzapine, 200 BID quetiapine, or 1 mg BID of risperidone). The maximum dose is 8 capsules a day administered in a BID schedule. BID dosing must be maintained, and it is recommended (but not required) that the larger dose be given in the evening when the split doses are not equal. Dose decreases may be at any time and at any dosing increment at the discretion of the study clinician.

In many cases the subject will enter the study on antipsychotic treatment. Here, the clinician may chose to simultaneously decrease the prior antipsychotic and increase the study antipsychotic (e.g. cross-titrate the medications). Less frequently, the clinician may chose to abruptly stop the prior antipsychotic and initiate the study antipsychotic. The study physician should use his or her best clinical judgment when making decisions about transition from prior antipsychotic to the study antipsychotic.

The following **initial** dosing schedule is recommended, but the clinician should individualize treatment in each subject based on tolerability and clinical response:

Day of Treatment	AM Dose	PM Dose
Day 1,2	---	1 capsule
Day 3,4	1 capsule	1 capsule
Day 5,6	1 capsule	2 capsules
Day 7,8	2 capsules	2 capsules

3.4.2.2. Discussion of Dosing Design

The dosing range was chosen to allow clinicians maximal flexibility in dosing each antipsychotic medication in first episode patients. The dosing range takes into the account that first episode patients, compared to patients with chronic schizophrenia, usually respond to lower doses of antipsychotic medication, and will be more likely to develop adverse effects if the highest dose range of the antipsychotic medication is used. The starting dose for the study antipsychotic is at the lower end of the therapeutic range in order to minimize the risk of adverse effects. The titration schedule is also chosen to minimize the risk of acute adverse effects, and to maximize initial tolerability of each medication. A more rapid titration rate could inflate discontinuation rates due to acute adverse effects, and thus potentially bias study results.

The rationale for BID dosing relates to the fact that quetiapine needs to be administered BID, although risperidone and olanzapine may be administered once a day. In order to maintain the study blind, it will be necessary to administer all drugs twice daily. Other options (e.g. a mosaic design) would result in at least a partial break of the blind. The disadvantage of the BID dosing is that previous studies have shown that medication adherence is enhanced with once daily versus more frequent medication dosing. Thus, the potential advantage of a once a day drug versus twice a day drug on all-cause pharmacologic treatment discontinuation will not be assessed in this study. In summary, the advantage of different dosing schedules for the three drugs is substantially outweighed by the disadvantage posed by breaking the study blind.

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3.4.2.3. Concomitant and Adjunctive Medication

i. Extrapyramidal side effects: Concomitant medication will be allowed for a limited time period of 2 weeks to treat emergent extrapyramidal side effects. Concomitant medication for extrapyramidal side effects will not be allowed for a cumulative total of more than 14 days over the course of the trial. **Clinicians are encouraged to respond to emergent EPS by reducing the dose of the study antipsychotic medication.** Benzodiazepine treatment for akathisia is included in this 14-day limit (but benzodiazepine use is not restricted for symptoms of anxiety or agitation.) The rationale for this strategy is that each of the antipsychotic medications included in this trial is reported to have an efficacious dose that is lower than the threshold dose that will induce EPS. Thus, clinicians will be encouraged to lower the dose of antipsychotic medication if EPS emerges. If the treating clinician determines that short-term EPS medication is needed to control the acute emergence of EPS, then benztropine will be allowed to treat Parkinsonian or dystonic symptoms, and propranolol or lorazepam to treat akathisia.

ii. Co-morbid disorders and symptoms: Other antipsychotic medications will be allowed only in those subjects who enter the study on an antipsychotic, and the clinician judges that cross-titration of old and study antipsychotic is clinically indicated. Other antipsychotics will not be allowed for treatment of agitation, anxiety, residual psychosis, or for any other reason. Antidepressants and mood stabilizers will not be allowed during the first 8 weeks of the trial to minimize the risk that individuals with primary mood disorders might be included in the protocol. After 8 weeks clinicians will be allowed to treat co-morbid Axis I disorders as clinically indicated. Clinicians will be allowed to treat co-morbid anxiety/agitation/insomnia as needed at any time during the study, with any appropriate medication (except that other antipsychotic medications are not allowed). Except as noted in this section, there are no restrictions on use of concomitant or adjunctive medications.

3.4.3. Method of Assigning Subjects to Treatment Groups

Subject eligibility will be established before treatment randomization. Subjects will be randomized by Quintiles IVR system to provide centralized randomization services during Phases 2. If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study. The Quintiles IVR system will randomize subjects into one of three treatment arms during Phase 2:

olanzapine (2.5-20 mg/day)

quetiapine (100-800 mg/day)

risperidone

Each bottle will be labeled with an ID number specific double blind label. Subjects will be assigned to an initial treatment kit during Phase 2 and re-supplied with additional treatment kits at each study visit. When a subject discontinues or completes the trial, all unused study medication will be returned to the investigative site for accountability and destruction as described in the Study Reference Manual.

3.4.4. Blinding and Procedures for Unblinding the Study

3.4.4.1. Methods for Insuring Blinding

This study aims to adhere to the principles of research design and conduct that ensure the integrity of studies and the validity of data derived from them. Laska and colleagues (1992) have written that, "As an abiding principle, RCTs designed for hypothesis testing should strive for the most rigorous blinding procedures possible in order to minimize the risk of compromising the study's integrity, which inevitably leads to uncertainties about the validity of inferences. This furthers the interest of the global community in enabling valid decision making." There is an obligation to all patients who participate in this study and to all those whose treatment will be influenced by the results of this study to implement the study in such a way that it produces valid results (i.e., a close approximation of truth).

3.4.4.2. Methods for Unblinding the Study

We also have a responsibility to individual patients participating in this study and to their treating clinicians to provide information from this study that will maximally inform treatment decisions. However, if we adopted a policy of providing unblinded information to all patients after their completion of this study we could jeopardize the results of this study.

Therefore, we have adopted a policy in which unblinded information will be provided only in those situations wherein the need for this information is substantial, that there is significant clinical risk to the patient should unblinding not occur. The unblinding information will be given only to medical care providers that are not affiliated with this study. Excepting medical emergency, at no time should any investigator or staff member associated with the study be unblinded. The policy requires application to the Study Trial Center, initiated by contact with the project Medical Office, by patients or their treating clinicians. Such situations may include, but are not limited to:

i. When a patient has dropped out or been withdrawn from the study and there is a concern for the patient's well being due to a serious adverse event that has placed the patient at grave medical risk.

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ii. When there is a desire to maintain a patient who has had an exceptionally favorable therapeutic outcome (e.g., if a patient has completed Phase 2).

Sites that strongly desire to unblind the treatment of a patient who has had a favorable outcome should send a brief (one-page) letter to Dr. Lieberman stating:

a) the specifics of the case that justifies unblinding and why they believe this option is important enough so that the individual patient's needs warrant risking the study's integrity;

b) the name and contact information of the treating clinician who will receive the unblinded treatment information;

c) how the site intends to restrict access to the unblinded information to only those clinicians who will care for a patient after completion of that patient's participation in the study, and restrict this information and any follow-up on this patient from study research staff at the site.

4. STUDY MEASUREMENTS AND ENDPOINTS

4.1. Safety Measurements and Endpoints

4.1.1. Adverse Events

4.1.1.1. Definitions

The definitions of adverse events (AEs), serious adverse events (SAE's) and other significant adverse events (OAE's) are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this at each site.

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or wash-out periods even if no study treatment has been administered.

4.1.1.2. Serious Adverse Events

The trial period is defined from the time that the informed consent document is signed until 30 days after administration of the last dose of the trial drug. All serious AEs occurring during the trial period (including death due to any cause) or within 30 days after

administration of the last dose of the trial drug must be communicated within 1 day of the investigator becoming aware of the event to the Quintiles' Safety Surveillance and Reporting office designated personnel, using the telephone or fax numbers provided in the Study Reference Manual. Any fatal or life threatening AEs must be reported to Quintiles' Safety Surveillance and Reporting office immediately, but no longer than 1 day from the time the investigator becomes aware of the event. A causality assessment must be provided for all serious AEs. Critical follow-up information on serious AEs must be provided as soon as it is available, but no longer than 1 day from the time the investigator became aware of the information. Other essential, but not critical, information may be reported within the following 5 days. Although it is important to report all serious AEs to Quintiles' Safety Surveillance and Reporting office designated personnel within 1 day, extra measures must be taken to ensure that any serious, unexpected, possibly drug-related AE be communicated immediately. AstraZeneca will be responsible for relaying appropriate information regarding serious AEs to the regulatory authorities.

A serious AE is defined as one that satisfies any of the following criteria:

- Results in death.
- Is immediately life-threatening, including potentially life threatening suicidal behavior or suicidal behavior that results in hospitalization.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

[Note: Hospitalization for symptoms related to schizophrenia, schizoaffective disorder, or schizophreniform disorder, such as psychosis or mood symptoms are an expected part of the disease and thus should not be recorded as a serious adverse event, but should be recorded as an adverse event.]

- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix A.

The causality of SAE's (i.e., their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the drug?" For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B.

4.1.1.3. Death

All deaths occurring within the trial period or within 30 days after the last dose of trial drug is given must be reported to Quintiles' Safety Surveillance and Reporting office within 1 day.

If the reason for withdrawal from the trial is death, this event may be reported as a serious AE. The cause of death should be documented on the appropriate CRF. An AE CRF should be completed for all conditions except objective progression of disease, and the event must be reported to Quintiles' Safety Surveillance and Reporting office as a serious AE within 1 day. The report should contain information regarding the co-involvement of progression of disease, if appropriate, and incorporate information regarding the primary and secondary causes of death. If an autopsy has been performed, results of the autopsy must be obtained and forwarded to Quintiles' Safety Surveillance and Reporting office along with any available toxicology reports.

4.1.1.4. Recording of Adverse Events

It is important to distinguish between serious and severe AE's. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.4.2.1 b). An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

Should a pregnancy occur it must be reported in accordance with the procedures described below. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAE's. Spontaneous miscarriages should also be reported and handled as SAE's. Elective abortions without complications should not be handled as AE's. All outcomes of pregnancy must be reported to Quintiles on the pregnancy outcomes report form.

4.1.1.5. Reporting of Serious Adverse Events

The process flow for reporting serious adverse events along with associated documents and contact information will be presented in the Study Reference Manual to accompany this protocol. The first report from the site of a serious adverse event will be made by phone and followed with facsimile (FAX). The investigator must provide the minimal information: i.e. trial number, subject's initials and date of birth, medication code number, period of intake, CRF I.D. number and nature of the adverse event and investigator's causality assessment. The sites' point of contact for SAE reporting will be Quintiles Drug Safety Surveillance and Reporting Office (contact information is provided in the Study Reference Manual). The sites

will also have the opportunity to make initial contact with the Project Medical Officer (PMO) also described in Study Reference Manual, for clarifying the event seriousness criteria.

This report of a serious adverse event by telephone must always be confirmed by a written, more detailed report. For this purpose, the sites will be provided with an AstraZeneca approved SAE Form for Clinical Trials, to be completed and signed by the Investigator. If a non-serious case becomes serious, this and other relevant information should also be provided to Quintiles' Safety Surveillance and Reporting office within 1 day as described in the paragraph above.

After initial notification, the Safety Surveillance and Reporting office will inform AstraZeneca designated personnel and the Project Medical Officer at UNC of the event. The Surveillance and Reporting office will be responsible for collecting source documents and confirming the seriousness, relationship to study product and expectedness. Narratives created by the Safety Surveillance and Reporting office and all supporting documentation will be sent to the PMO for medical review and to the sponsor at the same time. The PMO will review and acknowledge receipt of the report to Quintiles. The PMO will review the SAE in a timely fashion, and return the document to Quintiles if any changes are needed.

Surveillance and Reporting office will handle any questions needing follow-up with the site or the site monitor. Quintiles office will forward any follow-up information to AstraZeneca.

AstraZeneca will file the SAE reports via Clintrace Reporting and will assume responsibility for any necessary expedited reporting of adverse events to the authorities with concurrent notification to Quintiles and the investigators. It is the investigator's responsibility to report the AE's which are classified by the sponsor as serious, unlisted and associated with the use of the drug to the Independent Ethics Committee / Institutional Review Board (IEC/IRB) which has approved the protocol unless otherwise required and documented by the IEC/IRB.

All SAEs have to be reported, whether or not considered causally related to the investigational product. All SAEs will be recorded in the case report form. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

4.2. Measures of Assessment

4.2.1. Rationale for Assessment Measures

4.2.1.1. Clinical Assessments:

The primary outcome measure, "all-cause treatment discontinuation" is rated on the same measure developed for use in the CATIE trial. This rating form requires the clinician to date the phase discontinuation, and then to indicate whether the discontinuation was

"administrative" (e.g. the patient moved) or "clinical." A "clinical" discontinuation is then further rated as being either: 1) clinician decision inadequate therapeutic effect, 2) clinician decision unacceptable side effects, or 3) patient decision. Rating rules have been established for each of these 3 categories, and all raters will be required to pass certification in completing the ratings of "all-cause treatment discontinuation." Our experience with the CATIE trial indicates that a high level of reliability (kappa > .9) can be achieved and maintained in the use of this scale with our training program.

The clinical assessment tools, including the Positive and Negative Symptom Scale (PANSS), the Calgary Depression Rating Scale (CDRS), the Clinical Global Impressions (CGI), and the Alcohol Use Scale/Drug Use Scale (AUS/DUS), Symptom Onset in Schizophrenia (SOS) Scale, and the Structured Clinical Interview for DSMIV disorders have established reliability and validity. These instruments assess important domains of psychopathology in patients with schizophrenia and related psychotic disorders. The PANSS provides good coverage of positive, negative, and general psychopathology, but does not provide detailed information about mood symptoms. We included a more detailed assessment of mood symptoms (CDRS) due to the recognized importance of mood symptoms in schizophrenia, and the potential for atypical antipsychotics to impact mood. The AUS/DUS are single item questionnaires that provide information about severity of substance use problems. We included this domain to assess the interaction between adherence and severity of substance use.

Adverse effects will be thoroughly assessed by patient interview, ratings on extrapyramidal rating scales (AIMS, BARS, SA), and laboratory studies. Weight will be assessed through waist hip measurement, and direct assessments of weight. Adverse effects will be evaluated both by general and systematic inquiry. Extrapyramidal side effects will be evaluated by physical exam. Laboratory studies will include fasting glucose and lipid panels to evaluate impact of drugs on glucose tolerance and risk of hyperlipidemia. Hemoglobin A1c levels will be evaluated to further evaluate glucose metabolism. Prolactin, estrogen and testosterone will assess impact of drugs on these hormones. Other routine chemistries will be systematically assessed as well to evaluate general health.

Vital signs (systolic and diastolic blood pressure) will be measured at every visit up to and including week 12, week 24, week 52 and end of study.

A physical exam at screening will include an ophthalmologic exam for the detection of cataracts. This examination of the eyes will be repeated at six-month intervals and at the end of study.

3.4.1.2. Storage and Inventory Management

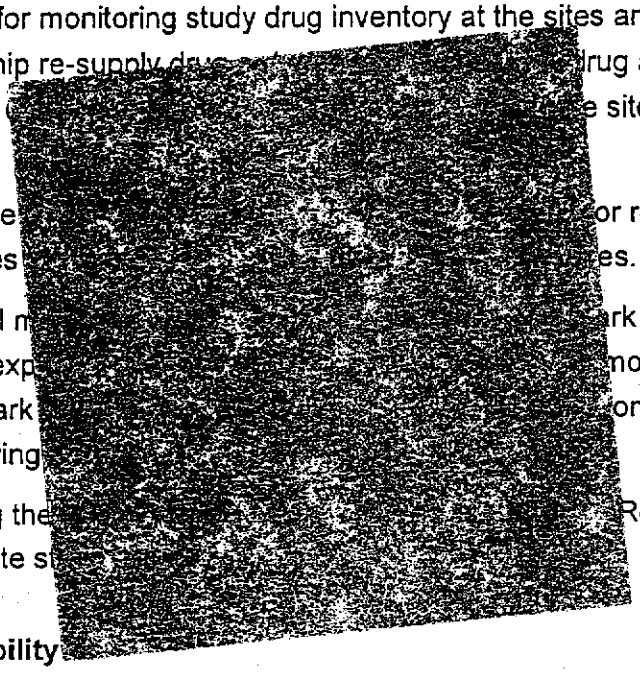
All product will be monitored in a secure, limited access area at controlled room temperature.

Quintiles will be responsible for monitoring study drug inventory at the sites and notifying the distribution center when to ship re-supply dru rug at the site falls below its re-order point, then e site up to its respective target level).

The Quintiles interactive voice or re-ordering study drug replacement boxes es.

The Quintiles IVR system will m rk drug as expired 60 days prior to the exp monitor drug expiration at the sites and mark on date to prevent a subject from receiving

Specific procedures for using the Reference Manual to be distributed at site s



3.4.1.3. Accountability

The investigator, his/her designee or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all trial supplies using the Drug Accountability Form. These forms must be available for inspection at any time. Trial drug prescription, dispensing and compliance will be captured on the case report forms and will be source validated by Quintiles monitors.

3.4.2. Doses and Treatment Regimens

3.4.2.1. Dosing and Administration

All subjects will begin with one capsule (olanzapine 2.5 mg, quetiapine 100 mg, risperidone .5 mg). During the first 6 weeks of treatment, medication may be increased by one capsule at the discretion of the clinician with a minimal period between dose increases of 48 hours. Dose increases should be made based on clinical response and tolerability, and it is recommended that the length of the dosing intervals be increased if the subject experiences medication side effects. The recommended initial target dose is 2 study pills BID (e.g. BID of olanzapine, 200 BID quetiapine, or 1 mg BID of risperidone). The maximum dose is 8 capsules a day administered in a BID schedule. BID dosing must be maintained, and it is recommended (but not required) that the larger dose be given in the evening when the split doses are not equal. Dose decreases may be at any time and at any dosing increment at the discretion of the study clinician.

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In many cases the subject will enter the study on antipsychotic treatment. Here, the clinician may chose to simultaneously decrease the prior antipsychotic and increase the study antipsychotic (e.g. cross-titrate the medications). Less frequently, the clinician may chose to abruptly stop the prior antipsychotic and initiate the study antipsychotic. The study physician should use his or her best clinical judgment when making decisions about transition from prior antipsychotic to the study antipsychotic.

The following **initial** dosing schedule is recommended, but the clinician should individualize treatment in each subject based on tolerability and clinical response:

Day of Treatment	AM Dose	PM Dose
Day 1,2	---	1 capsule
Day 3,4	1 capsule	1 capsule
Day 5,6	1 capsule	2 capsules
Day 7,8	2 capsules	2 capsules

3.4.2.2. Discussion of Dosing Design

The dosing range was chosen to allow clinicians maximal flexibility in dosing each antipsychotic medication in first episode patients. The dosing range takes into the account that first episode patients, compared to patients with chronic schizophrenia, usually respond to lower doses of antipsychotic medication, and will be more likely to develop adverse effects if the highest dose range of the antipsychotic medication is used. The starting dose for the study antipsychotic is at the lower end of the therapeutic range in order to minimize the risk of adverse effects. The titration schedule is also chosen to minimize the risk of acute adverse effects, and to maximize initial tolerability of each medication. A more rapid titration rate could inflate discontinuation rates due to acute adverse effects, and thus potentially bias study results.

The rationale for BID dosing relates to the fact that quetiapine needs to be administered BID, although risperidone and olanzapine may be administered once a day. In order to maintain the study blind, it will be necessary to administer all drugs twice daily. Other options (e.g. a mosaic design) would result in at least a partial break of the blind. The disadvantage of the BID dosing is that previous studies have shown that medication adherence is enhanced with once daily versus more frequent medication dosing. Thus, the potential advantage of a once a day drug versus twice a day drug on all-cause pharmacologic treatment discontinuation will not be assessed in this study. In summary, the advantage of different dosing schedules for the three drugs is substantially outweighed by the disadvantage posed by breaking the study blind.

3.4.2.3. Concomitant and Adjunctive Medication

i. Extrapyramidal side effects: Concomitant medication will be allowed for a limited time period of 2 weeks to treat emergent extrapyramidal side effects. Concomitant medication for extrapyramidal side effects will not be allowed for a cumulative total of more than 14 days over the course of the trial. **Clinicians are encouraged to respond to emergent EPS by reducing the dose of the study antipsychotic medication.** Benzodiazepine treatment for akathisia is included in this 14-day limit (but benzodiazepine use is not restricted for symptoms of anxiety or agitation.) The rationale for this strategy is that each of the antipsychotic medications included in this trial is reported to have an efficacious dose that is lower than the threshold dose that will induce EPS. Thus, clinicians will be encouraged to lower the dose of antipsychotic medication if EPS emerges. If the treating clinician determines that short-term EPS medication is needed to control the acute emergence of EPS, then benztropine will be allowed to treat Parkinsonian or dystonic symptoms, and propranolol or lorazepam to treat akathisia.

ii. Co-morbid disorders and symptoms: Other antipsychotic medications will be allowed only in those subjects who enter the study on an antipsychotic, and the clinician judges that cross-titration of old and study antipsychotic is clinically indicated. Other antipsychotics will not be allowed for treatment of agitation, anxiety, residual psychosis, or for any other reason. Antidepressants and mood stabilizers will not be allowed during the first 8 weeks of the trial to minimize the risk that individuals with primary mood disorders might be included in the protocol. After 8 weeks clinicians will be allowed to treat co-morbid Axis I disorders as clinically indicated. Clinicians will be allowed to treat co-morbid anxiety/agitation/insomnia as needed at any time during the study, with any appropriate medication (except that other antipsychotic medications are not allowed). Except as noted in this section, there are no restrictions on use of concomitant or adjunctive medications.

3.4.3. Method of Assigning Subjects to Treatment Groups

Subject eligibility will be established before treatment randomization. Subjects will be randomized by Quintiles IVR system to provide centralized randomization services during Phases 2. If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study. The Quintiles IVR system will randomize subjects into one of three treatment arms during Phase 2:

olanzapine (2.5-20 mg/day)

quetiapine (100-800 mg/day)

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risperidone (

Each bottle will be labeled with an ID number specific double blind label. Subjects will be assigned to an initial treatment kit during Phase 2 and re-supplied with additional treatment kits at each study visit. When a subject discontinues or completes the trial, all unused study medication will be returned to the investigative site for accountability and destruction as described in the Study Reference Manual.

3.4.4. Blinding and Procedures for Unblinding the Study

3.4.4.1. Methods for Insuring Blinding

This study aims to adhere to the principles of research design and conduct that ensure the integrity of studies and the validity of data derived from them. Laska and colleagues (1992) have written that, "As an abiding principle, RCTs designed for hypothesis testing should strive for the most rigorous blinding procedures possible in order to minimize the risk of compromising the study's integrity, which inevitably leads to uncertainties about the validity of inferences. This furthers the interest of the global community in enabling valid decision making." There is an obligation to all patients who participate in this study and to all those whose treatment will be influenced by the results of this study to implement the study in such a way that it produces valid results (i.e., a close approximation of truth).

3.4.4.2. Methods for Unblinding the Study

We also have a responsibility to individual patients participating in this study and to their treating clinicians to provide information from this study that will maximally inform treatment decisions. However, if we adopted a policy of providing unblinded information to all patients after their completion of this study we could jeopardize the results of this study.

Therefore, we have adopted a policy in which unblinded information will be provided only in those situations wherein the need for this information is substantial, that there is significant clinical risk to the patient should unblinding not occur. The unblinding information will be given only to medical care providers that are not affiliated with this study. Excepting medical emergency, at no time should any investigator or staff member associated with the study be unblinded. The policy requires application to the Study Trial Center, initiated by contact with the project Medical Office, by patients or their treating clinicians. Such situations may include, but are not limited to:

i. When a patient has dropped out or been withdrawn from the study and there is a concern for the patient's well being due to a serious adverse event that has placed the patient at grave medical risk.

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ii. When there is a desire to maintain a patient who has had an exceptionally favorable therapeutic outcome (e.g., if a patient has completed Phase 2).

Sites that strongly desire to unblind the treatment of a patient who has had a favorable outcome should send a brief (one-page) letter to Dr. Lieberman stating:

a) the specifics of the case that justifies unblinding and why they believe this option is important enough so that the individual patient's needs warrant risking the study's integrity;

b) the name and contact information of the treating clinician who will receive the unblinded treatment information;

c) how the site intends to restrict access to the unblinded information to only those clinicians who will care for a patient after completion of that patient's participation in the study, and restrict this information and any follow-up on this patient from study research staff at the site.

4. STUDY MEASUREMENTS AND ENDPOINTS

4.1. Safety Measurements and Endpoints

4.1.1. Adverse Events

4.1.1.1. Definitions

The definitions of adverse events (AEs), serious adverse events (SAE's) and other significant adverse events (OAE's) are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this at each site.

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or wash-out periods even if no study treatment has been administered.

4.1.1.2. Serious Adverse Events

The trial period is defined from the time that the informed consent document is signed until 30 days after administration of the last dose of the trial drug. All serious AEs occurring during the trial period (including death due to any cause) or within 30 days after

administration of the last dose of the trial drug must be communicated within 1 day of the investigator becoming aware of the event to the Quintiles' Safety Surveillance and Reporting office designated personnel, using the telephone or fax numbers provided in the Study Reference Manual. Any fatal or life threatening AEs must be reported to Quintiles' Safety Surveillance and Reporting office immediately, but no longer than 1 day from the time the investigator becomes aware of the event. A causality assessment must be provided for all serious AEs. Critical follow-up information on serious AEs must be provided as soon as it is available, but no longer than 1 day from the time the investigator became aware of the information. Other essential, but not critical, information may be reported within the following 5 days. Although it is important to report all serious AEs to Quintiles' Safety Surveillance and Reporting office designated personnel within 1 day, extra measures must be taken to ensure that any serious, unexpected, possibly drug-related AE be communicated immediately. AstraZeneca will be responsible for relaying appropriate information regarding serious AEs to the regulatory authorities.

A serious AE is defined as one that satisfies any of the following criteria:

- Results in death.
- Is immediately life-threatening, including potentially life threatening suicidal behavior or suicidal behavior that results in hospitalization.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

[Note: Hospitalization for symptoms related to schizophrenia, schizoaffective disorder, or schizophreniform disorder, such as psychosis or mood symptoms are an expected part of the disease and thus should not be recorded as a serious adverse event, but should be recorded as an adverse event.]

- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix A.

The causality of SAE's (i.e., their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the drug?" For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B.

4.1.1.3. Death

All deaths occurring within the trial period or within 30 days after the last dose of trial drug is given must be reported to Quintiles' Safety Surveillance and Reporting office within 1 day.

If the reason for withdrawal from the trial is death, this event may be reported as a serious AE. The cause of death should be documented on the appropriate CRF. An AE CRF should be completed for all conditions except objective progression of disease, and the event must be reported to Quintiles' Safety Surveillance and Reporting office as a serious AE within 1 day. The report should contain information regarding the co-involvement of progression of disease, if appropriate, and incorporate information regarding the primary and secondary causes of death. If an autopsy has been performed, results of the autopsy must be obtained and forwarded to Quintiles' Safety Surveillance and Reporting office along with any available toxicology reports.

4.1.1.4. Recording of Adverse Events

It is important to distinguish between serious and severe AE's. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.4.2.1 b). An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

Should a pregnancy occur it must be reported in accordance with the procedures described below. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAE's. Spontaneous miscarriages should also be reported and handled as SAE's. Elective abortions without complications should not be handled as AE's. All outcomes of pregnancy must be reported to Quintiles on the pregnancy outcomes report form.

4.1.1.5. Reporting of Serious Adverse Events

The process flow for reporting serious adverse events along with associated documents and contact information will be presented in the Study Reference Manual to accompany this protocol. The first report from the site of a serious adverse event will be made by phone and followed with facsimile (FAX). The investigator must provide the minimal information: i.e. trial number, subject's initials and date of birth, medication code number, period of intake, CRF I.D. number and nature of the adverse event and investigator's causality assessment. The sites' point of contact for SAE reporting will be Quintiles Drug Safety Surveillance and Reporting Office (contact information is provided in the Study Reference Manual). The sites

will also have the opportunity to make initial contact with the Project Medical Officer (PMO) also described in Study Reference Manual, for clarifying the event seriousness criteria.

This report of a serious adverse event by telephone must always be confirmed by a written, more detailed report. For this purpose, the sites will be provided with an AstraZeneca approved SAE Form for Clinical Trials, to be completed and signed by the Investigator. If a non-serious case becomes serious, this and other relevant information should also be provided to Quintiles' Safety Surveillance and Reporting office within 1 day as described in the paragraph above.

After initial notification, the Safety Surveillance and Reporting office will inform AstraZeneca designated personnel and the Project Medical Officer at UNC of the event. The Surveillance and Reporting office will be responsible for collecting source documents and confirming the seriousness, relationship to study product and expectedness. Narratives created by the Safety Surveillance and Reporting office and all supporting documentation will be sent to the PMO for medical review and to the sponsor at the same time. The PMO will review and acknowledge receipt of the report to Quintiles. The PMO will review the SAE in a timely fashion, and return the document to Quintiles if any changes are needed.

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All SAEs have to be reported, whether or not considered causally related to the investigational product. All SAEs will be recorded in the case report form. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

4.2. Measures of Assessment

4.2.1. Rationale for Assessment Measures

4.2.1.1. Clinical Assessments:

The primary outcome measure, "all-cause treatment discontinuation" is rated on the same measure developed for use in the CATIE trial. This rating form requires the clinician to date the phase discontinuation, and then to indicate whether the discontinuation was

"administrative" (e.g. the patient moved) or "clinical." A "clinical" discontinuation is then further rated as being either: 1) clinician decision inadequate therapeutic effect, 2) clinician decision unacceptable side effects, or 3) patient decision. Rating rules have been established for each of these 3 categories, and all raters will be required to pass certification in completing the ratings of "all-cause treatment discontinuation." Our experience with the CATIE trial indicates that a high level of reliability (kappa > .9) can be achieved and maintained in the use of this scale with our training program.

The clinical assessment tools, including the Positive and Negative Symptom Scale (PANSS), the Calgary Depression Rating Scale (CDRS), the Clinical Global Impressions (CGI), and the Alcohol Use Scale/Drug Use Scale (AUS/DUS), Symptom Onset in Schizophrenia (SOS) Scale, and the Structured Clinical Interview for DSMIV disorders have established reliability and validity. These instruments assess important domains of psychopathology in patients with schizophrenia and related psychotic disorders. The PANSS provides good coverage of positive, negative, and general psychopathology, but does not provide detailed information about mood symptoms. We included a more detailed assessment of mood symptoms (CDRS) due to the recognized importance of mood symptoms in schizophrenia, and the potential for atypical antipsychotics to impact mood. The AUS/DUS are single item questionnaires that provide information about severity of substance use problems. We included this domain to assess the interaction between adherence and severity of substance use.

Adverse effects will be thoroughly assessed by patient interview, ratings on extrapyramidal rating scales (AIMS, BARS, SA), and laboratory studies. Weight will be assessed through waist hip measurement, and direct assessments of weight. Adverse effects will be evaluated both by general and systematic inquiry. Extrapyramidal side effects will be evaluated by physical exam. Laboratory studies will include fasting glucose and lipid panels to evaluate impact of drugs on glucose tolerance and risk of hyperlipidemia. Hemoglobin A1c levels will be evaluated to further evaluate glucose metabolism. Prolactin, estrogen and testosterone will assess impact of drugs on these hormones. Other routine chemistries will be systematically assessed as well to evaluate general health.

Vital signs (systolic and diastolic blood pressure) will be measured at every visit up to and including week 12, week 24, week 52 and end of study.

A physical exam at screening will include an ophthalmologic exam for the detection of cataracts. This examination of the eyes will be repeated at six-month intervals and at the end of study.

4.2.1.2. Other Clinical Outcomes

Aspects of social and occupational functioning will be evaluated with the Heinrichs-Carpenter Quality of Life Scale (QOL). We will examine impact of insight as measured by the Insight into Treatment and Attitudes Questionnaire (ITAQ) on treatment adherence.

4.2.1.3. Neurocognitive Function (120 minute battery)

See the Appendix C (section 7.3) for detailed description of the neurocognitive battery. Neurocognitive impairment is associated with various aspects of schizophrenia symptoms. Patients with more severe cognitive deficits tend to have more severe negative symptoms, symptoms of disorganization, and worse adaptive dysfunction (Tollefson et al., 1997; Beasley, Tollefson, et al., 1996; Beasley, Sanger, et al., 1996). While the correlations between severity of general cognitive deficits and positive symptoms may be weak, some aspects of cognitive impairment, such as working memory, may also be associated with the severity of positive symptoms (Blin, Azorin & Bouhours, 1996). Most importantly, the severity of cognitive deficits in schizophrenia is associated with various aspects of poor outcome, such as the inability to acquire skills, poor social problem-solving, and poor community functioning (Tollefson et al., 1997; Ceskova & Svestka, 1993). In fact, cognitive impairment may be a better predictor of poor outcome than any other symptom domain (Green, 1996).

Nearly 50 years of research has indicated that typical antipsychotics provide little benefit to the cognitive disturbances of patients with schizophrenia (Chouinard et al., 1993). However, atypical antipsychotic medications may improve cognitive performance in patients with schizophrenia. Clozapine (Hoyberg et al., 1993; Claus et al., 1992), risperidone (Peuskens, 1995; Marder & Meibach, 1994; Min et al., 1993, and olanzapine (Purdon et al., 2000; Tran et al., 1997), are associated with improved cognitive performance in patients with schizophrenia. In a recent meta-analysis significant improvement in cognition was found with the atypical antipsychotics even when the results of each study were corrected for multiple comparison (Keefe et al., 1999). Data published after this meta-analysis was completed suggest that olanzapine and quetiapine may have cognitive-enhancing properties that are at least as substantial as those reported with risperidone and clozapine (Purdon et al., 2000; Meltzer & McGurk, 1999; Reinstein et al., 1999). None of the studies published to date have investigated the impact of atypical antipsychotic medications on cognitive deficits in patients with first episode psychosis, and only two have investigated the cognitive effects of quetiapine. Finally, further study is needed to determine the extent that the observed neurocognitive treatment effects are independent of changes in symptoms, side effects, or anticholinergic use.

Despite the importance of cognitive deficits in the assessment and treatment of schizophrenia, there are no easily administered cognitive scales to assess patients with

schizophrenia. In contrast to assessment of patients with schizophrenia, cognitive function in patients with dementia is usually assessed with one of several widely-available cognitive questionnaires (e.g., Mini Mental Status Examination, Dementia Rating Scale, Alzheimer's Disease Assessment Scale). These questionnaires can be easily administered at the patient's bedside and are routinely employed in the screening of progressive neurological disorders. The administration of these tests can help shed light on the global severity of the cognitive deficits that the patient exhibits, track progression, and measure symptom changes. The Brief Assessment of Cognition in Schizophrenia (BACS) is a brief clinician administered neurocognitive battery (30 minutes). The BACS will be administered in this study to evaluate the usefulness of this brief battery in first episode schizophrenia. The availability of a quick and efficient tool for measuring the cognitive profile of a patient with schizophrenia will be an extremely useful guide to the clinician making decisions about the potential rehabilitation of the schizophrenic patient. Further, this tool may be used to assess efficiently and effectively the extent to which cognitive deficits improve in the course of treatment with novel antipsychotic medication.

4.2.2. Quality Control of Clinical and Functional Assessments

Effort spent at minimizing measurement error is rewarded by increase in study power (Blackwelder, 1982). In designing the training program for the clinical and functional assessments, we considered both burden on the sites, and the potential gain in reliability of ratings. There will be a web based training program for all clinical and functional assessments developed and maintained by the UNC coordinating team. An initial training will be done at the study initiation meeting. Clinical and functional raters who do not attend the study initiation meeting will receive their training based on completion of the web based training program, supplemented with telephone meetings.

For key outcomes, specifically "all-cause pharmacologic treatment discontinuation," the PANSS, and for the SCID (used to determine study eligibility) raters will participate in certification procedures. Certification for "all-cause pharmacologic treatment discontinuation" will use case vignettes, and certification will be given when a rater demonstrates excellent (kappa>.9) agreement with the gold standard ratings. Similarly, certification for the SCID will use SCID based case vignettes, and require good agreement (kappa > .8) with the gold standard ratings. Certification for the PANSS will involve rating 3 video-taped interviews, and obtaining a passing score (ICC>.7). Raters who do not initially pass certification will be offered remedial training and an opportunity to re-take the certification evaluation. In addition, additional training will be offered during the course of the study during monthly telephone conferences.

We will require maintenance training on these key outcome measures, in order to minimize the risk of interviewer drift. The intensity of the maintenance training is based on the

difficulty of scale, and the risk of interviewer drift. For both the SCID and for "all-cause treatment discontinuation" annual re-certification is adequate to maintain reliable ratings. For the PANSS, given the complexity of this scale, more frequent training is needed, and with ratings of PANSS tapes three times a year, and calculation of reliability (based on the 3 tapes) annually.

5. Statistical Analyses:

5.1. Introduction

This statistical analysis plan concentrates primarily on the analysis of effectiveness data, with a brief mention of safety data. A more elaborate statistical analysis plan (SAP) exists as a separate document.

5.2. Study Objectives and Endpoints

5.2.1. Study Objectives

Study objectives are to compare the three groups with respect to measures of effectiveness, safety, and tolerability.

5.2.2. Primary Objective

The primary objective is to compare the effectiveness of quetiapine versus risperidone and olanzapine, on the primary response variable of "all-cause pharmacologic treatment discontinuation." Each comparison (quetiapine versus risperidone, and quetiapine versus olanzapine) will be tested to show that quetiapine is not inferior to each respective comparator (Blackwelder 1982). For each subject, the primary response variable will be whether that subject discontinued the study or study medication for any cause from phase 2 of the trial prior to week 52.

5.2.3. Secondary Objectives

The secondary objectives are to compare the three groups with respect to other measures of effectiveness, measures of tolerability, and measures of safety.

5.2.4. Study Endpoints and Evaluations

All-cause pharmacologic treatment discontinuation is a binary variable defined as follows: Any subject who has discontinued the trial or study medication prior to week 52 will be considered to have met the criteria. Only those subjects who have stayed on study medication through 52 weeks will be considered as having not met the criteria. Consequently, discontinuation includes events such as withdrawal due to adverse event,

lost to follow-up, administrative reasons, and withdrawal due to non-efficacy. Note that this primary response variable is defined in such a way that there can be no missing data.

Secondary endpoints include reason for "all cause pharmacological discontinuation," change in psychopathology [measured with the total, positive, and negative symptom scales of the Positive and Negative Symptom Scale (PANSS)], change in depressive symptoms [measured with the Calgary Depression Rating Scale (CDRS)], global psychopathology [measured with the Clinical Global Impression (CGI) scale], and substance abuse [measured with the Alcohol Use Scale /Drug Use Scale (AUS/DUS)].

Analysis of safety measures will be covered later, but safety will be assessed using physical exams, systematic ratings, laboratory studies, and assessment of adverse events (AEs). Laboratory measures will include fasting glucose and lipid panels, hemoglobinA1c, prolactin, estrogen (women) or testosterone (men) and other routine blood chemistries.

Neurocognitive function will be assessed a battery of neurocognitive tests described elsewhere in the protocol.

The schedule of assessments and evaluations is given in section 3 of the protocol.

5.3. Analysis Populations and Datasets

5.3.1. Definitions of Analysis Populations

The following populations are defined as the analysis populations

1. Intent-To-Treat (ITT) population: All subjects randomized to a treatment and who took at least one dose of post-randomization study medication.
2. Modified ITT population (MITT): All subjects in the ITT population who received at least one post-randomization set of evaluation. This MITT population is necessary because while the primary effectiveness variable can be assessed using the ITT population, all secondary effectiveness and most safety variables need a post-randomization assessment.
3. Evaluable cohort: All subjects in the MITT population who received at least 12 weeks of treatment, and received the week 12 evaluations.
4. Safety Cohort: The ITT population. The intention is to evaluate safety using all available data. It is possible that a subject might discontinue due to AE or SAE prior to the first post-randomization evaluation, and not return for further evaluations. For these subjects, the only safety responses available will be reported AE or SAE. For all other safety evaluations, subjects need to be in the ITT population to be evaluable for safety.

5.3.2. Application of Analysis Populations

The ITT population will be used for evaluation of the primary effectiveness variable, all-cause pharmacologic treatment discontinuation, and for evaluation of AE or SAE information, where available. The MITT population will be used for all secondary effectiveness variables, including neurocognitive and social assessments, and for all safety variables. The evaluable cohort will be used for all effectiveness and safety evaluations of baseline to week 12 data. The safety cohort will be used for all safety analyses, except those that can be done using the ITT population.

5.3.3. Definition of Analysis Datasets

Two versions of the datasets will be used for many of these analyses: an observed cases (OC) and a last observation carried forward (LOCF) dataset. For the primary effectiveness variable, defined in a way that precludes missing data, there is no need to handle missing data.

5.3.4. Application of the Analysis Datasets

Each dataset will include flags for each observation, for each occasion, indicating whether that observation is to be included in the ITT, MITT, Evaluable Cohort, or Safety Cohort datasets. These flags will be used to select appropriate populations for analysis.

5.4. Data Quality and Assurance

Data entry, management, quality assurance, and quality control will be performed by the CRO, Quintiles Transnational.

5.5. Statistical Considerations

5.5.1. General Statistical Procedures

All analyses described in this protocol are *a priori* planned analyses. Other analyses will be exploratory, designed and run *post hoc*. All analyses will be designated as planned or exploratory in reports and articles. Unless stated otherwise, all statistical tests will be two-tailed tests using a significance level of 0.05, except possibly for tests used to make decisions about covariates or blocking factors. In the event that some centers fail to enroll sufficient numbers of observations, small centers will be pooled together into analysis centers using an algorithm described in sections 5.7.2 and 5.7.3.5.

5.5.2. Patient Enrollment and Disposition

Patient disposition will be summarized by treatment group and by analysis population. Numbers and percentages of completers and dropouts will be listed, by treatment group and analysis population. For all dropouts, the reason for dropout will be listed.

7. Appendices

7.1. (Appendix A) Further Guidance On The Definition Of An SAE

Results in death

Any death resulting from an AE occurring during the trial period or within 30 days after the last dose of the trial drug is given. However, should a death be reported to an investigator at any time following the completion or discontinuation/withdrawal of a subject from the trial, including any protocol required post-treatment follow-up, the investigator has an obligation to report the serious AE to Quintiles' Safety Surveillance and Reporting office if the investigator feels it is related to study drug.

Life threatening

The subject must have been at an immediate risk of dying from the AE as it occurred or it was suspected that use or continued use of the product would result in the subject's death. This does not include events that might have caused death if they had occurred in a more serious form (e.g., drug-induced hepatitis that resolves without hepatic failure).

Hospitalization

Any AE resulting in hospital admission and usually an overnight stay. The term "prolongs hospitalization" means delayed planned or anticipated discharge date (again usually by at least 1 overnight stay). Hospital admissions and/or surgical operations planned before or during a trial are not considered AEs if the illness or disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected way during the trial. In addition, for this study, hospitalizations due to exacerbation of the symptoms of schizophrenia, schizoaffective disorder, or schizophreniform disorder will not be considered SAEs. Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). For the purpose of this trial, hospitalizations for social reasons, respite care, elective treatment or surgery, or lack of efficacy will not be regarded as serious AEs.

Results in persistent or significant disability or incapacity

Any AE resulting in impairment of, damage to, or disruption in the subject's body function, structure, or both; physical activities; or quality of life.

Important medical event/medical intervention

Medical and scientific judgment should be exercised in deciding whether an event is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity, but may jeopardize the patient or may require medical intervention to prevent 1 or more outcomes listed in the definition of a serious event. These should usually be considered serious. Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by acetaminophen overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

Discontinuation of the trial treatment or of routine administration of prescription medications, or changes in their dosages should not be considered medical intervention.

The following information is the minimum that must be provided to Quintiles' Safety Surveillance and Reporting office within 24 hours for each serious event (see Study Reference Manual for fax and telephone numbers):

- Trial number.
- Center number.
- Subject number.
- Subject initials.
- AE.
- Seriousness.
- Causality assessment.
- Date of onset.
- Study drug dose or amount.

The following additional information must be provided to Quintiles' Safety Surveillance and Reporting office as soon as it is available:

- Event intensity.
- Outcome (plus date of resolution if available).
- Withdrawal statement (yes or no).
- Concurrent therapy (identify treatment for AE).
- Date of birth and sex.
- Other current illnesses.
- Relevant medical history.
- Date and cause of death (if applicable).

This information should be captured on forms that AstraZeneca will provide. These forms should then be faxed to Quintiles' Safety Surveillance and Reporting office.

Should a serious AE be reported to an investigator at any time following the completion or discontinuation/withdrawal of a subject from the trial, including any protocol required post-

treatment follow-up, the investigator has an obligation to report the serious AE to Quintiles' Safety Surveillance and Reporting office if the investigator feels it is related to study drug.

7.2. (Appendix B) A Guide to Interpreting the Causality Question

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this.

7.3. (Appendix C) Neurocognitive Assessment Battery

A battery of tests designed to assess treatment-related improvement should meet the following criteria: reliability in patients with schizophrenia, statistical properties that allow significant improvement in most schizophrenic patients, and suggestions from previous data that they may be responsive to specific atypical antipsychotic treatment (Davidson and Keefe, 1995; Keefe et al, 1999). The battery of tests proposed for this study will not only meet these criteria, but it will also include the tests that are the battery for the Neurocognitive Assessment Unit for the CATIE Project. This battery of tests was decided upon by the CATIE Project's Neurocognitive Advisory Group.

Despite the importance of cognitive deficits in the assessment and treatment of schizophrenia, there are no easily administered cognitive scales to assess patients with schizophrenia. In contrast to assessment of patients with schizophrenia, cognitive function in patients with dementia is usually assessed with one of several widely available cognitive questionnaires (e.g., Mini Mental Status Examination, Dementia Rating Scale, Alzheimer's Disease Assessment Scale). These questionnaires can be easily administered at the patient's bedside and are routinely employed in the screening of progressive neurological disorders. The administration of these tests can help shed light on the global severity of the cognitive deficits that the patient exhibits, track progression, and measure symptom changes. The availability of a quick and efficient tool for measuring the cognitive profile of a patient with schizophrenia will be an extremely useful guide to the clinician making decisions about the potential rehabilitation of the schizophrenic patient. Further, this tool may be used to assess efficiently and effectively the extent to which cognitive deficits improve in the course of treatment with novel antipsychotic medication.

The neurocognitive battery for this study will include such an instrument. The Brief Assessment of Cognition in Schizophrenia (BACS) is a recently developed short battery of tests devised for bedside administration by non-psychologists. This 20-25 minute battery is specifically designed to measure treatment-related improvements, and includes alternate forms. It is in the process of being assessed for reliability, validity, and equivalence of forms. The battery includes brief assessments of executive functions, verbal fluency, attention, memory, working memory and motor speed.

Non-cognitive Assessments

The following assessments will be completed at the baseline visit: education level; parental education level; a brief examination of English competency; and previous experience with the tests in the neurocognitive battery.

Neurocognitive Assessments

The following battery is to be completed according to the following schedule: baseline, 12 weeks, and end of the study. The tests will be given in the order listed. Estimated time of test administration is in parentheses. Each test and the measures to be derived from it are described below. This battery also includes the primary measures that have thus far been shown to be responsive to quetiapine:

Verbal fluency (10)
Mazes (5)
Letter-Number Test (5)
Hopkins Verbal Learning Test (10)
Facial Emotion Discrimination Task (10)
Digit-Symbol (3)
Grooved Pegboard (5)
Computerized Continuous Performance Tests (10)
Computerized Spatial Working Memory test (10)
Computerized Wisconsin Card Sorting Test (20)
BACS (30)
Total time: 120 minutes

The neurocognitive functions and the recommended tests to measure them for the schizophrenia trial are described here. The tests are not described in order of administration.

Verbal fluency. Verbal fluency is severely impaired in psychotic disorders and patients with dementia. One of the most robust findings in a recent meta-analysis of the effect of atypical antipsychotic medication on cognition was the improvement of verbal fluency (Keefe et al, 1999). Even after the analyses from all studies were corrected for multiple comparisons, four of six studies demonstrated significant improvement on verbal fluency measures with clozapine. Verbal fluency improvement has also been reported with quetiapine (Velligan and Miller, 1999; Purdon et al, in press).

Controlled Oral Word Association Test (COWAT). Subjects are asked to generate as many words as possible within a given letter category (F, A, or S) in each of three 60-second trials. Measures: number of correct words generated in each category.

Category instances. In three separate trials, subjects are given 60 seconds to generate as many words as possible within the categories of animals, fruits, and vegetables. Measures: number of correct words generated in each category.

Working memory. Working memory has been described as a fundamental aspect of cognition (Goldman-Rakic, 1987). Recent developments in the understanding of prefrontal functions in humans have followed extensive work on the neural circuitry underlying working memory function and dysfunction. Although conventional antipsychotics block dopamine receptors in the prefrontal cortex, which has been found to impair working memory functions in nonhuman primates under normal conditions (Sawaguchi and Goldman-Rakic, 1994),

they do not impair or improve working memory functions in patients with schizophrenia (see reviews by Cassens et al 1990; Medalia et al, 1988; Goldberg and Weinberger, 1996). The evidence to support clozapine-related enhancement of working memory functions is weak. While one study reported improvement in all cognitive tests, including auditory consonant trigrams, with clozapine treatment (Galletly et al, 1997), other work suggests that treatment with clozapine does not improve verbal working memory as assessed by auditory consonant trigrams (Hagger et al, 1993; Lee et al, 1994) or digits backward (Grace et al, 1996). Risperidone may improve aspects of working memory functions (Green et al, 1997; Rossi et al, 1997; Meltzer and McGurk, 1999). The effect of quetiapine or olanzapine on working memory functions has not been adequately assessed to date.

Letter-number test of auditory working memory (Gold, et al, 1997). Patients are presented auditorily with clusters of letters combined with numbers (e.g., N6G2). They are asked to reorder the cluster and tell the experimenter the numbers first, from lowest to highest, then the letters in alphabetical order. Measure: number of correct sequences.

Computerized test of visuospatial working memory (Hershey et al, 1999). Subjects must focus on a central fixation cross on a computer screen. While fixated, a cue appears for 150 ms in one of 32 possible locations at a 4.5 inch radius from the central fixation. A 15 sec delay period is then imposed. During the delay, a series of geometric shapes appear in place of the fixation cross. The subject must press the spacebar whenever the diamond shape appears. After the delay, the fixation cue returns, and the subjects must to point on the computer screen where they remember seeing the cue. On the cue-present trials the cue is present during the response phase. This set of trials gives an indication of subjects' pointing accuracy. Mean error in mm (distance between recall and actual target) is calculated for each subject for each type of trial. There are 8 delay trials and 8 cue-present trials. Measures: mean error for each type of trial.

Verbal learning and memory. Verbal memory is severely impaired in schizophrenia (Saykin et al, 1991), and is significantly associated with outcome (Green, 1996). When correcting for multiple comparisons in the small-sample studies completed to date, none of the nine studies assessing verbal memory demonstrated significant improvements with atypical medication (Keefe et al, 1999). However, recent data collected on small samples suggest that quetiapine may improve verbal memory (Velligan and Miller, 1999; Purdon et al, 2000). Improvement in verbal memory would be of great value. Verbal memory is most often assessed with measures of recall of stories or lists of words. An important feature of memory testing in longitudinal treatment studies is the use of alternate forms to minimize confusion between practice effects and genuine treatment effects. Alternate forms are available for tests of verbal memory and learning of lists of words.

Hopkins Verbal Learning Test. This test consists of 12 nouns read aloud for three consecutive trials, each trial followed by a free-recall test. The test has six alternate forms. Patients will receive the forms in a counter-balanced order. If patients receive the test more than six times, the order will continue as from the first testing session. Measures: number of items recalled on each trial.

Social Cognition Performance on cognitive tests of facial emotion discrimination and identification has been found to be associated with a variety of social outcomes (Mueser et al 1997). Despite the importance of these cognitive measures, no data has assessed their response to pharmacologic treatment.

Face Emotion Discrimination Task (FEDT; Kerr & Neale, 1993). Facial affect discrimination will be assessed with the Face Emotion Discrimination Task. The FEDT requires the subject to determine whether two faces presented next to one another are expressing the same or different emotion. Thirty pairs of target faces are presented to the patient. Measures: the number of faces correctly discriminated.

Motor function. Motor functions have been found to improve with clozapine (Myer-Lindenberg et al, 1997) and risperidone (Gallhoffer et al, 1996). Data comparing olanzapine, haloperidol and risperidone suggest that olanzapine may improve motor functions more than either haloperidol or risperidone (Purdon et al, 2000). In addition to the direct measures of motor function in studies of atypical antipsychotic effects on cognition, the cognitive functions that are most responsive to atypical antipsychotics have a timed component. This pattern may be a result of the absence of EPS from atypical antipsychotic medications compared to conventional antipsychotics. Since timed tests all involve some degree of dependence upon motor skills, which are impaired by EPS, the advantage of quetiapine could partially be a result of the reduced EPS. Thus, it is important to include tests of motor functions in the battery. Furthermore, motor functions are related to outcome (Bilder et al, 1985), underscoring the importance of this domain. A grooved Pegboard test will be used to measure motor function, a computerized reaction time test will be used to measure motor speed, and the Digit-Symbol subtest of the WAIS-R will be used to measure a related construct, graphomotor speed. The symbol-digit and digit-symbol tests have been among the most responsive tests to atypical antipsychotic treatment (Keefe et al, 1999).

Wechsler Adult Intelligence Score - Revised (WAIS-R) Digit Symbol Test. Each numeral (1 through 9) is associated with a different simple form. Patients are given a list of numerals and are asked to copy as many forms associated with the numerals as possible in 90 seconds. Measure: raw score.

Grooved Pegboard. Patients are asked to insert in a specified order 25 pegs with keys into a pegboard with randomly positioned slots. Two 45-second trials will be completed with the dominant hand. Measure: average number of pegs successfully inserted.

Attention. Attention is a fundamental cognitive deficit in patients with schizophrenia (Neuchterlein and Dawson, 1984) and is associated with outcome in patients with schizophrenia (Green, 1996). It is one of the few measures that demonstrates some improvement with typical antipsychotic medications (Medalia et al, 1988; Blyler and Gold, in press). In previous studies, attention has been found to improve with risperidone (Stip and Lussier, 1996; Rossi et al, 1997; Kern et al, 1998), clozapine (Zahn et al, 1994; Grace et al, 1996), olanzapine (Purdon et al, in press; Meltzer and McGurk, 1999), and quetiapine (Sax et al, 1998). Attention is traditionally measured with a Continuous Performance Test (CPT).

Continuous Performance Test (CPT). The Identical Pairs version of the CPT (Cornblatt et al, 1988) has high test-retest reliability, making it ideal for studies with repeated assessments. In this study, we recommend a version of the CPT that includes three 150-trial conditions of increasing difficulty. This procedure will assure that data can be collected on even the most cognitively impaired patients, yet no patients will perform perfectly in the hardest condition Each condition involves the presentation of stimuli on a computer screen at the rate of one per second. In the first condition, two-digit numbers are presented, and the subject lifts his or her finger whenever the two-digit number is a repeat of the previous two-digit number. The second and third conditions are the same as the first condition, except that the numbers are three-digits and four-digits respectively. This test will be administered on a computer with a high-resolution monitor and an external mouse. Measure: d' for each condition.

Executive function.

Wisconsin Card Sorting Test (Heaton et al, 1993) (64-card version). Performance on the Wisconsin Card Sorting Test (WCST) has been found to improve with clozapine, risperidone, and olanzapine, although many negative findings have been reported (reviewed in Meltzer and McGurk, 1999). This area of cognition is particularly challenging in clinical trials with repeated assessments since a usual component of a measure of executive function is to learn the rules of the test. Once these rules are learned, they are often remembered, even after a long (e.g. six month) delay period. This issue is highlighted through the use of the Wisconsin Card Sorting Test (WCST). Subjects sort a series of stimulus cards by matching them to four "key cards" that differ by form, color and number. Successful performance on the WCST depends upon learning how to sort the cards and how to switch the sorting strategy when appropriate, since the "correct" sorting strategy changes after 10 consecutive correct responses. There is some controversy as to whether patients with schizophrenia benefit from previous exposures to the WCST. An early study with very chronic subjects suggested that patients with schizophrenia did not learn from previous assessments with the WCST (Goldberg et al, 1987). However, data from patients with heterogeneous cognitive performance (Green et al, 1990) suggest that the performance of many patients with schizophrenia does improve with repeated exposure to the test. This issue may be particularly important in this project, since the mechanism by which atypical

antipsychotic medications improve cognition may be related to the improvement of episodic memory, which may help patients recall how they performed the test on previous testing sessions. Subcortical dopaminergic blockade may inhibit this improvement (Robbins, 1990; Robbins et al, 1990). This notion has recently been supported by data suggesting that schizophrenic patients treated with risperidone continue to benefit from repeated exposure to a test of processing capacity, while patients treated with haloperidol are limited in the gains they receive from additional administrations of the test (Harvey, in press). Thus, the sole use of a test such as the WCST to measure executive functions in this study may lead to confusion between improvements in executive function and improvements in episodic memory. Furthermore, differences in performance resulting from the different atypical medications may be difficult to detect if a sizable percentage of patients learn the test well enough to perform at near-perfect levels. Thus, a 64-card version of the WCST will be used in this study to minimize learning effects. This test will be administered on computer to minimize scoring errors. A 64-card computerized version of the WCST is now available commercially, and has been used with success by us in a industry trial currently underway. Measures: number of perseverative errors; completed number of categories and additional consecutive cards in the final category.

WISC-III Mazes. Another test of executive functions will also be administered for this trial. The performance of patients with schizophrenia on maze tasks, usually impaired in schizophrenia, has been found to be improved with risperidone (Gallhoffer et al, 1996). In this test, patients use a pencil to attempt to draw through a series of 9 mazes without entering into blind alleys. Performance is timed. Measure: raw score.

Brief Assessment of Cognition (BACS):

The neurocognitive assessment tool for this study will be the Brief Assessment of Cognition in Schizophrenia (BACS). This battery is brief (approximately 30 minutes), and is devised for easy administration and scoring by non-psychologists. The battery is specifically designed to measure treatment-related improvements, and includes alternate forms. It is in the process of being assessed for reliability, validity, and equivalence of forms. The battery includes brief assessments of executive functions, verbal fluency, attention, verbal memory, working memory and motor speed.

List Learning (Verbal Memory): Patients are presented with 15 words and then asked to recall as many as possible. This procedure is repeated 5 times. There are alternate forms.

Measure: number of words recalled per trial. Time: 7 minutes.

Digit Sequencing Task (Working Memory): Patients are presented with clusters of numbers of increasing length. They are asked to tell the experimenter the numbers in order, from lowest to highest.

Measure: number of correct responses. Time: 5 minutes.

Token Motor Task (Motor Speed): Patients are given 100 plastic tokens and asked to place them into a container as quickly as possible for 60 seconds.

Measure: the number of tokens placed into the container. Time: 3 minutes.

Category Instances (Semantic Fluency): Patients are given 60 seconds to name as many words as possible within a given category. Controlled Oral Word Association Test (Letter Fluency): In two separate trials, patients are given 60 seconds to generate as many words as possible that begin with a given letter.

Measure: number of words generated per trial. Time: 5 minutes.

Tower Test (Executive Functions) Patients look at two pictures simultaneously. Each picture shows 3 different-colored balls arranged on 3 pegs, with the balls in a unique arrangement in each picture. The patient gives the total number of times the balls in one picture would have to be moved in order to make the arrangement of balls identical to that of the other, opposing picture. There are alternate forms.

Measure: number of correct responses. Time: 7 minutes.

Symbol Coding (Attention and Motor Speed) As quickly as possible, patients write numerals 1-9 as matches to symbols on a response sheet for 90 seconds.

Measure: number of correct items. Time: 3 minutes.

Additional Test at the baseline visit: Estimated Premorbid Intelligence with Reading Score

To estimate the relative premorbid intelligence of the patients in each sample, patients will receive the Wide Range Achievement Test-3, Reading subtest (WRAT-3).

To complete this test, patients simply read aloud a series of letters and words of increasing difficulty. If for some reason, this test can not be completed at the baseline visit, it can be completed on a subsequent visit. Measure: Number of words and letters successfully pronounced.

Quality Control of Neurocognitive Data

Specific procedures for test administration and scoring will be detailed in a neurocognitive manual. Each test battery will be scored by two experienced testers. Data will be reviewed via fax and emailed files for all neurocognitive assessments. If data quality is not perfect for the first five assessments, neurocognitive testing and scoring procedures will be reviewed via a site visit.

Site Training

Each neurocognitive tester will receive extensive training on test administration. Testers will be required to demonstrate testing competence and complete knowledge of the test procedures specific to this study before they are permitted to initiate testing. If not already completed in previous studies, the testing environment will also be assessed, and testing will not be permitted to begin without an appropriate space for neurocognitive evaluation. Although the testers may differ in the amount of education and testing experience they report, all testers must have previous experience with some of the tests in the battery. In addition, all testers who do not have a doctorate in psychology will be supervised by a Ph.D. psychologist at their site.

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7.4. (Appendix D) Schedule of Assessments:

7.4.1. Phase 1 (Screening) and Phase 2 (52-week treatment)

Measures	Visit:	Screen	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	EOS
	Week in Treatment:	-2 to 0	0	1	2	3	4	5	6	8	10	12	16	20	24	28	32	36	40	44	48	52/ EOP	EOS
Informed Consent		X																					
Medical History, PE (including eye exam)		X																					
Screening demographics		X																					
Socioeconomic status (SES)			X																				
Psychiatric Diagnosis (SCID), Psychiatric History, Abbreviated PANSS (P1, P2, P3, P5, P6)		X																				X	X
SOS, PAS			X																				
One year completion status																						X	
End of Study/Reason for All Cause Pharmacological Treatment Discontinuation																							X
Randomization (Inclusion/Exclusion)			X																				
Clinical Global Impressions (CGI)		X	X	X	X	X										X	X	X	X	X	X	X	X
Adverse Events/Side Effects			X	X	X	X										X	X	X	X	X	X	X	X
Medical Diagnosis			X	X	X	X										X	X	X	X	X	X	X	X
Medication Adherence				X	X	X										X	X	X	X	X	X	X	X
Other Medication Record			X	X	X	X										X	X	X	X	X	X	X	X
Weight			X	X	X	X											X	X	X	X	X	X	X
Positive and Negative Symptom Scale (PANSS)			X	X	X												X	X	X	X	X	X	X
Calgary Depression Rating Scale (CDRS)			X	X	X												X	X	X	X	X	X	X
Alcohol Use Scale/Drug Use Scale (AUS/DUS)			X				X										X	X	X	X	X	X	X
Health Care Service Utilization			X				X										X	X	X	X	X	X	X
Abnormal Involuntary Movements (AIMS)/ Barnes Akathisia/Simpson-Angus,			X	X	X		X										X	X	X	X	X	X	X
Psychoeducational Intervention				X		X																	
Fasting glucose, fasting lipid panel, Hbg A1c			X																			X	X
Prolactin, estrogen or testosterone			X																			X	X
LFTs, BUN, creatinine, chemistries, CBC, urinalysis		X													X							X	X
Vitals		X	X	X	X	X	X	X							X							X	X
Eye Exam		X													X							X	X
waist/hip, height			X									X			X							X	X
Hair analysis			X												X							X	X
Heinrichs-Carpenter Quality of Life Scale (HQQL) (Deficit Syndrome rating included at V0, V19/EOS			X									X			X							X	X
Insight into Treatment and Attitudes Questionnaire (ITAQ)			X									X			X							X	X
Neurocognitive			X									X										X	X

Eliminated with 2nd Phase III Schedule

7.4.2. Phase III (Optional Double-blind follow-up)

Measures / Visit:	20	21	22	23/EOS	EOS
Month since last visit:	1	1	1	1	1
End of Study/Reason for Treatment Discontinuation				X	X
Clinical Global Impressions (CGI)	X		X	X	X
Adverse Events/Side Effects/Medical Diagnoses		X		X	X
Medication Adherence	X	X	X	X	X
Concomitant/adjunctive medication, patient summary		X		X	X
Weight		X		X	X
Positive and Negative Symptom Scale (PANSS)		X		X	X
Calgary Depression Rating Scale (CDRS)		X		X	X
Alcohol Use Scale/Drug Use Scale (AUS/DUS)	X	X	X	X	X
Health Care Service Utilization				X	X
Barnes Akathisia, Simpson-Angus, Abnormal Involuntary Movements (AIMS)				X	X
Fasting glucose, fasting lipid panel, HgbA1c				X	X
Vitals				X	X
waist/hip, height				X	X
Heinrichs-Carpenter Quality of Life Scale (HQQL)				X	X
Insight into Treatment and Attitudes Questionnaire (ITAQ)				X	X

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