Protocol: MK-0777 for the Treatment of Cognitive Impairments in Patients with Schizophrenia

Treatment Units for Research of Neurocognition in Schizophrenia (TURNS)
PI: Stephen R. Marder, MD

Sponsor: NIMH
Project Officer: Ellen Stover, Ph.D.

Study PI: Robert W. Buchanan, M.D.  Maryland Psychiatric Research Center

Site PIs:
Robert Buchanan, MD  Maryland Psychiatric Research Center
John Csernansky, MD  Washington University Medical Center
Donald Goff, MD  Massachusetts General Hospital
Daniel Javitt, MD  Nathan Kline Institute
Jeffrey Lieberman, MD  Columbia University Medical Center
Stephen R. Marder, MD  UCLA
Joseph McEvoy, MD  Duke
Larry J. Seidman, Ph.D.  Lemuel Shattuck Hospital/ Beth Israel Deaconess Medical Center

Version: 2.1
Rev: 04/22/08

Protocol: MK-0777 for the Treatment of Cognitive Impairments in Patients with Schizophrenia
Schizophrenia

Justification:

Patients with schizophrenia are characterized by a broad range of neurocognitive abnormalities. These include impairments in attention, including abnormalities in sensory gating; executive function; visual and verbal learning and memory; working memory; processing speed; and social cognition (Nuechterlein et al, 2004). These impairments are major determinants of poor functional outcome in patients with schizophrenia (Green, 1996; Green et al, 2004). Conventional antipsychotics have limited effects on these impairments. Second generation antipsychotics may have modest benefits for cognitive function, but whether this represents a direct cognitive enhancing effect has not been established. Regardless, patients continue to exhibit pronounced cognitive impairments despite adequate second generation antipsychotic treatment. Adjunctive pharmacotherapy may offer a viable approach for the treatment of cognitive impairments. Adjunctive agents can be used to modulate specific neurotransmitter systems that are hypothesized to be involved in the pharmacology of cognitive functions.

Gamma-amino-butyric acid (GABA) is the major inhibitory neurotransmitter in the CNS. GABAergic mechanisms are important for the regulation of prefrontal cortical function and they are thought to play a major role in working memory, through their modulation of glutamatergic function in the dorsolateral prefrontal cortex (DLPFC). GABAergic interneurons (chandelier cells) release GABA, which inhibits pyramidal neuron output by binding to GABA_A α2 subunit of GABA receptors on the axon initial segment.

There is a growing body of evidence to suggest that there is altered GABA function in schizophrenia. Post-mortem studies of schizophrenia have demonstrated altered expression of glutamic acid decarboxylase (GAD_67), an enzyme involved in the synthesis of GABA (Akbarian et al, 1995; Volk et al, 2000; Guidotti et al, 2000; Vawter et al, 2002). A microarray study found that there was decreased expression of genes encoding for GABA-related proteins (Mirmics et al, 2000). The reduction in GAD_67 appears to be restricted to chandelier cells in middle cortical layers (Volk et al, 2000; Hashimoto et al, 2003). In subjects with decreased GAD_67, there is also a decrease in the mRNA levels for the GABA reuptake transporter (Volk et al, 2001) and a decrease in the density of chandelier cell connections with the axon initial segment of pyramidal cells (Woo et al, 1998; Pierri et al, 1999). Finally, there appears to be a marked increase in the density of the GABA_A α2 subunit on the axon initial segment (Volk et al, 2002).

The results of the post-mortem investigation of the GABAergic system suggest that there is a marked decrease in GABAergic inhibition of pyramidal cell glutamatergic transmission in the DLPFC of patients with schizophrenia (Lewis et al, 2005). This disturbance in GABAergic function may have important implications for our understanding of cognitive impairments in schizophrenia. Specifically, intact GABAergic function has been shown to be required for normal working memory (Wilson et al, 1994; Rao et al, 1999; Rao et al, 2000). Patients with schizophrenia have been shown to have a broad range of marked working memory impairments (Park et al, 1992; Gold et al, 1997; Callicott et al, 1998, 1999; Carter et al, 1998; Tek et al, 2001; Neuechterlein et al, 2004). Working memory may also subserve a number of other cognitive processes, so that improvement of working memory function may also lead to improvement in other domains of cognitive function. GABAergic agents that increase GABA inhibition of
cortical pyramidal cells would be hypothesized to improve the working memory and possibly other cognitive impairments in patients with schizophrenia.

A number of previous studies have examined the efficacy and safety of benzodiazepines in patients with schizophrenia (Wolkowitz and Pickar, 1990; Carpenter et al, 1999). Benzodiazepines are nonselective allosteric agonists that bind to GABA\(_A\) \(\alpha_1\), \(\alpha_2\), \(\alpha_3\) and \(\alpha_5\) receptor subunits. These studies were primarily designed to evaluate the efficacy of benzodiazepines for residual positive symptoms, the prevention of relapse, and the treatment of acute psychotic episodes. In general, benzodiazepines were found to be safe and effective for the treatment of acute episodes and the prevention of relapse (Carpenter et al, 1999), with less efficacy for the treatment of residual positive symptoms (Wolkowitz and Pickar, 1990). None of these studies evaluated the efficacy of benzodiazepines for cognitive impairments. The major concern with the use of benzodiazepines is their abuse potential and their sedative effects.

MK-0777 is a GABA\(_A\) \(\alpha_2/\alpha_3\) partial agonist. MK-0777 is functionally selective for the \(\alpha_2\) and \(\alpha_3\) subunits, with virtually no activity for the \(\alpha_1\) and \(\alpha_5\) subunits. Therefore, it is less likely to cause the level of sedation observed with benzodiazepines, which act at the \(\alpha_1\) subunit. MK-0777 has no known activity at any other receptor. In animal studies, MK-0777 was observed to cause less sedation, interact less with alcohol, and exhibit less abuse potential and physical dependence than benzodiazepines. There are two MK-0777 formulations: i) immediate release (IR); and ii) controlled-release formulation (Gel Extrusion Module, GEM). The MK-0777 GEM formulation will be used in the proposed study.

MK-0777 was developed as a treatment for Generalized Anxiety Disorder, but development was terminated because of the observation that MK-0777 caused cataracts in rodent long-term toxicology assays. There are no documented cases of MK-0777 causing cataracts in humans, but subjects will be monitored for cataracts throughout the proposed study. In clinical studies, both the MK-0777 IR and MK-0777 GEM formulations were well tolerated. The most common side effects (prevalence greater than 5%) included: constipation; dry mouth; flatulence; nausea; increased appetite; dizziness; disturbance in coordination; and insomnia (see Investigator Brochure). There are no previous preclinical or clinical studies of its potential cognitive enhancing properties. There is an ongoing pilot study evaluating the efficacy and safety of MK-0777 in patients with schizophrenia (P.I.: David A. Lewis, M.D.; University of Pittsburgh School of Medicine).

The standard of care for schizophrenia is antipsychotic medications to treat psychotic symptoms. However, cognitive impairments remain and these impairments have been found to be significantly associated with the poor psychosocial function observed in patients with schizophrenia. There is a considerable preclinical rationale for the use of drugs that act at the GABA\(_A\) \(\alpha_2\) subunit as adjunctive treatments to target cognitive impairments. MK-0777 provides an opportunity to directly test this mechanism.

As the main inhibitory neurotransmitter in the mammalian brain, GABA mediates inhibitory postsynaptic inhibition currents through the activation of ionotropic GABA\(_A\) receptors. The inhibitory currents can be recorded as oscillatory activities in neuronal and field recordings, and are thought to be involved in perceptual and cognitive processes. In the clinical trial, we will take two approaches to the delineation of possible oscillatory electrical biomarkers of MK-0777 activity at the GABA\(_A\) \(\alpha_2/\alpha_3\) receptor subtypes. The first paradigm involves a steady state auditory evoked potential (SSAEP), using auditory stimulus trains to elicit synchronized oscillations in the corresponding frequencies. Several lines of evidence suggest
that neural oscillations are very sensitive to GABA_A receptor manipulations. The steady state paradigm aims to establish which oscillatory frequency is more likely affected by MK-0777. Secondarily we can determine how specific neuropsychological domains are correlated with oscillatory changes induced by MK-0777. The second paradigm uses auditory mismatch negativity (MMN). MMN is a widely studied ERP component that indexes auditory information processing deficits at the level of auditory cortex. MMN is elicited when a series of repetitive stimuli is interrupted infrequently by a physically different deviant stimulus. These possible evoked potential biomarkers will be evaluated in drug-placebo comparisons and for dose-effects. We hypothesize that MK-0777, as a GABA_A α2/α3 partial agonist, will enhance higher frequency oscillations in the beta and gamma ranges, and that changes in neural oscillation will correspond to changes in cognitive functions. A 5 minute resting EEG will also be recorded.

**Purpose:**

The purpose of the proposed study is to examine the efficacy and safety of two doses of MK-0777 GEM, 3 mg BID and 8 mg BID, in the treatment of cognitive impairments in patients with schizophrenia. Secondary goals are to determine whether MK-0777 has beneficial effects on measures of functional capacity and patient self-report of cognitive function.

**Inclusion Criteria:**

1. Diagnosis: DSM-IV/DSM-IV-TR schizophrenia (including disorganized (295.10), paranoid (295.30), undifferentiated (295.90), and catatonic (295.20) subtypes)
2. Gender: Males and Females
3. Age: 18 - 60
4. Caucasian or Non-Caucasian
5. Capable of providing informed consent
6. Duration of illness equal to or greater than one year
7. Subjects will be treated with one of the following second generation antipsychotics: risperidone, paliperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole for the previous two months, with no change in dose in the last month.
8. Subjects will meet the following symptom criteria:
   a. Brief Psychiatric Rating Scale (BPRS) Hallucinatory Behavior or Unusual Thought Content item scores ≤ 5
   b. BPRS Conceptual Disorganization item score ≤ 4
   c. Simpson-Angus Scale total score ≤ 6
   d. Calgary Depression Scale total score ≤ 10
9. Subjects will meet the following cognitive performance criteria:
   a. Performance less than the maximum cutoff (in parentheses) for ONE of the following MCCB tests: i.) Letter-number span (20); ii.) HVLT total (31); and iii.) CPT d-prime (3.47)
   b. Able to complete the baseline MCCB validly as assessed by Chief Neuropsychologist or NP tester
   c. Raw score of 6 or greater on the WTAR
Exclusion Criteria:

1. Current treatment with conventional antipsychotics (e.g. fluphenazine, haloperidol) or clozapine
2. Current treatment (within 4 weeks) with psychotropic agents known to act at the GABA<sub>A</sub> receptor, including benzodiazepines; sedative-hypnotics other than trazadone and chloral hydrate; carbamazepine, gabapentin, lamotrigine, and valproic acid
3. Current treatment (within 4 weeks) with a drug that inhibits CYP3A4, including: cimetidine; cyclosporine; erythromycin or erythromycin-like drugs (e.g., azithromycin, clarithromycin); diltiazem; fluoxetine, fluvoxamine; itraconazole, ketoconazole or other systemic antifungal agents in the azole class; nefazodone; or induce CYP3A4, including: carbamazepine, modafinil; phenobarbital; phenytoin; rifampin; St. Johns wort; and troglitazone.
4. Current treatment (within 4 weeks) with psychotropic agents known to effect cognition: amphetamine; barbiturates; lithium; MAOIs; methylphenidate
5. Current treatment (within 4 weeks) with herbal preparations with possible psychotropic effects (e.g., St. Johns wort, kava-kava, Valerian, S-Adenosyl Methionine [SAMe])
6. Current treatment (within 4 weeks) with systemic steroids
7. Subjects with a DSM-IV diagnosis of alcohol or substance abuse (other than nicotine) within the last month or a DSM-IV diagnosis of alcohol or substance dependence (other than nicotine) within the last 6 months
8. LOCS III posterior subcapsular cataract grade of 1.0 or greater.
9. Uveitis with 1+ or greater flare or cells
10. Nuclear or cortical cataracts, if the severity of the cataracts is not appropriate for the age of the subject. This determination will be made by the examining ophthamologist.
11. Subjects with a history of significant head injury/trauma, as defined by one or more of the following:
   a. Loss of consciousness (LOC) for more than 1 hour
   b. Recurring seizures resulting from the head injury
   c. Clear cognitive sequellae of the injury
   d. Cognitive rehabilitation following the injury
12. Subjects with a history of clinically significant neurological, metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, and/or urological disorders (e.g. unstable angina, decompensated congestive heart failure, CNS infection or history of HIV seropositivity), which would pose a risk to the patient if they were to participate in the study or that might confound the results of the study. Active medical conditions that are minor or well controlled are not exclusionary if they do not affect risk to the patient or the study results. For example, the following are not exclusionary: a) stable and well controlled hypertension (BP normally <160/95 for at least 3 months); b) asthma (no serious attacks in the past year); c) hypothyroidism (T4 within normal limits for at least 1 year); and d) Type II diabetes (subjects with a reported HgbA1c outside of normal limits within the last 6 months should be reviewed with the study site investigator).
13. Clinically significant abnormalities in physical examination, ECG, or laboratory
assessments

14. A positive test for Hepatitis C antibody with concurrent evidence of impaired hepatic function (increased AST or ALT greater than 2 times the upper limit of normal) or positive tests for Hepatitis A antibody IgM fraction or Hepatitis B surface antigen, irrespective of the AST or ALT values.

15. Pregnant women or women of child-bearing potential, who are either not surgically-sterile or using appropriate methods of birth control

16. Women who are breast-feeding

17. History of severe symptoms of benzodiazepine withdrawal (e.g., history of seizures or delirium associated with withdrawal)

18. Patient has received ECT treatment within the last 3 months

19. Prior participation in a clinical trial of any other psychotropic medication within 2 months

Research Design:

The study will be conducted in the Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) study network, which is comprised of seven sites: Columbia University School of Medicine (P.I.: Jeffrey Lieberman, M.D.); Duke University School of Medicine (P.I.: Joseph McEvoy, M.D.); Harvard University School of Medicine (P.I.: Donald Goff, M.D.); Maryland Psychiatric Research Center (MPRC) (P.I.: Robert W. Buchanan, M.D.); Nathan Kline Institute (P.I.: Daniel Javitt, M.D.) University of California Los Angeles School of Medicine (P.I.: Steve Marder, M.D.); and Washington University School of Medicine (P.I.: John Csernansky, M.D.). The TURNS is a NIMH-funded contract for the evaluation of new compounds for the treatment of cognitive impairments in schizophrenia (HHSN 27820044 1003C; P.I.: Steve Marder, M.D.).

The proposed study is a multicenter, randomized, double-blind comparison of MK-0777 GEM 3 mg BID, MK-0777 GEM 8 mg BID, and placebo. The total sample will consist of 90 clinically stable patients with DSM-IV-TR schizophrenia, with 30 subjects randomized to each group. A best estimate diagnostic approach will be utilized, in which information from the Structured Clinical Interview for DSM-IV (First et al, 1997) is supplemented by information from family informants, previous psychiatrists, and medical records to generate a diagnosis. The projected number of subjects to be recruited from each site is 12-13. There will be a 2-week, placebo lead-in evaluation phase, in which subjects will undergo baseline diagnostic; medical, including a physical examination, EKG, CBC, complete metabolic panel, urine toxicology, and UA; psychiatric; and neurocognitive, symptom level and functional capacity and patient self-report of cognitive function assessments. In addition, all subjects will receive a slit-lamp eye examination and EEG/ERP procedures. At the end of the evaluation phase, subjects will be randomized to one of two MK-0777 doses or placebo. The double-blind treatment phase will be 4 weeks. Subjects will receive bi-weekly symptom assessments and weekly side effect and vital sign assessments. At week 4, subjects will undergo repeat administration of the neuropsychological test battery, EEG/ERP, and the functional capacity and patient self-report of cognitive function measures. These assessments will be done over a two-day period. Subjects will have blood samples collected for antipsychotic and MK-0777 levels at week 4. An EKG...
will be obtained at the end of the double-blind study. Slit-lamp eye examinations will be conducted at study completion, 6 months and 12 months after study completion. After the completion of the 4-week double-blind phase, there will be a 4-day follow-up phase during which subjects will be tapered off study medication.

Subjects may be treated with any second generation antipsychotic other than clozapine. Subjects must have been treated with the same antipsychotic for 2 months, with no change in dose for the previous month. Subjects who are receiving concurrent medications, other than benzodiazepines or GABAergic compounds, will be able to remain on those medications during the course of the study. If a subject is receiving other medications, they must be on the same dose for the previous month.

**Procedures:**

**Clinical Assessments:** The symptom assessments will include the Brief Psychiatric Rating Scale; Scale for the Assessment of Negative Symptoms (SANS); Calgary Depression Scale (CDS); and Clinical Global Impression Scale (CGI).

i) **BPRS:** the four positive symptom items - conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content - will be used to measure positive psychotic symptoms.

ii) **SANS:** the SANS total score, minus the global items, inappropriate affect, poverty of content of speech, and attention items, will be used to measure negative symptoms. The inappropriate affect, poverty of content of speech, and attention items are excluded as lacking construct validity and because factor analytic study results suggest that these items are not closely related to negative symptoms.

iii) **CDS:** the CDS total score will be used to measure depressive symptoms.

iv) **CGI:** the CGI severity of illness item will be used to assess global changes

**Safety Assessments:** The safety assessments will include the Simpson-Angus Extrapyramidal Symptom Rating Scale (SAS); Abnormal Involuntary Movement Scale (AIMS); and Side Effect Checklist (SEC).

i) **SAS:** a modified 11-item version of the SAS will be used to assess EPS.

ii) **AIMS:** is a 12-item scale, with 7 items designed to assess abnormal facial, oral, extremity, and trunk movements; 3 global judgement items; and 2 current dental status items.

iii) **SEC:** is designed to assess vital signs, commonly occurring antipsychotic side effects, and side effects indicative of uveitis or cataracts.

Subjects will be asked about adverse events at each visit, and instructed to call the study site should they experience adverse events at any point in the study. Any serious adverse event, including death due to any cause, which occurs to any subject entered into this study or within 14 days following cessation of treatment, whether or not related to the investigational product, will be reported to Merck & Co., Inc. within 24 hours.

**Functional Assessments:** The functional assessments will include the UCSD Performance-Based Skills Assessment (UPSA) and the Schizophrenia Cognition Rating Scale (SCoRS).

i) **UPSA:** is designed to assess skills in five areas: household chores, communication,
finance, transportation, and planning recreational activities. Subjects are asked to perform tasks in each of these areas and scored according to their ability to complete the task. The UPSA takes 25 - 30 minutes to administer.

ii) SCoRS: is a rating scale designed to elicit information from the subject and informant on the level of cognitive function of the subject. The subject and informant versions both have 20 items. Subject and informant interviews take from 10 - 15 minutes to complete.

**Neurocognitive Assessments: **The NIMH MATRICS Neuropsychological Battery, the Wechsler Test of Adult Reading (WTAR), the N-Back test; and the Continuous Performance Test (CPT-AX) will be used to assess cognitive function. The NIMH MATRICS Neuropsychological Battery is comprised of measures of: a) working memory; b) attention/vigilance; c) verbal memory; d) visual memory; e) processing speed; f) problem solving; and g) social cognition. The MATRICS battery is designed to be completed in 90 minutes or less. The N-Back and CPT-AX are both computerized measures of prefrontal cortex dependent cognitive behavior. The N-Back is a working memory test, in which the working memory load can be varied. Three conditions will be used: 0-back condition; 1-back condition; and 2-back condition. In the 0-back condition, the subject is asked to respond to the presentation of a prespecified target letter (e.g. “X”). In the 1-back condition, the subject is asked to respond to the second of two consecutive, identical letters. In the 2-back condition, the subject is asked to respond if a letter is identical to a letter presented two trials previous to the current letter presentation. In the CPT-AX, the subject is required to respond to a target letter (e.g. “X”) every time the “X” is preceded by an “A”. They are not to respond to an “X” if it preceded by a letter other than “A”. They are also not to respond to the letter following an “A” if it is not an “X”.

**General EEG and ERP Procedures:** Measurements will be obtained at baseline and repeated at the end of the trial. For ERP recording (EEG/ERP), participants will be asked to wear a cap with metal disks and to listen to different sets of sounds while reclining comfortably. Following testing, the cap will be removed and the gel will be washed off with water. The total duration of the EEG/ERP assessment is about 1.5 hours, including 1 hour of recording and 30 minutes to put on the cap and to remove it. Sixty-four channels will be used if available; otherwise, 32 channels will be used. Each electrode array should include M1, M2, and nose. Sounds will be presented via TDH headphones or hearing tubes. Eprime, Presentation, or Stim2 will be used for stimulus presentation. Recordings will be made with Neuroscan or Biosemi amplifiers.

1. **SSAEP and Resting EEG:** At each measurement occasion, EEG will be obtained under baseline conditions (5-min resting EEG) and in response to steady state auditory stimuli presented at 10, 20, and 40 Hz, approximately representing the alpha, beta, and gamma bands. The stimulations are 72-db clicks presented as a click train in the respective frequencies. Each 20 and 40 Hz click train lasts for 500ms with 700ms inter-train intervals. The 10 Hz train lasts for 800 ms because it needs more time to entrain the brain to the slower frequency. Stimulations are arranged in blocks. Each block contains 200 click trains of the same frequency. The presentation order of the blocks is randomized. The testing time is 13 minutes. The analysis will focus on evoked potential power and phase synchronization of respective oscillatory frequencies at the frontal region.

2. **MMN.** MMN will be elicited using an “optimized” paradigm (Naatanen et al., 2004)
in which multiple deviants types are included within a single auditory sequence. Deviant types to be used include pitch, duration and intensity. During data collection sessions, patients will be distracted from auditory stimuli by performing a visual distractor task, which will permit assessment as well of visual potentials (e.g. P1), which have recently been shown to be reduced in amplitude in schizophrenia. Auditory stimuli will be presented at 300 ms SOA. Each deviant type (pitch, duration, intensity) will be presented with 10% sequential probability. Because standards and deviants are presented within the same sequence, no control task is needed. Total time for task administration is approximately 30 min. Primary outcome measure is MMN to stimulus deviance, analyzed using rmMANOVA across deviance type with within subject factor of treatment. Secondary measures include amplitudes of P1 and P3 to the visual stimuli within the distractor task. If significant MMN effects are observed, exploratory analysis will be conducted to determine relative effects for each of the deviance manipulations.

Screening: The diagnosis of schizophrenia will be confirmed by a research psychiatrist using a modified version of the Structured Clinical Interview for DSM IV (SCID). The BPRS, SANS, CDRS and SAS will be administered to verify that inclusionary criteria are met. Subjects will have a slit-lamp eye examination.

2-Week, Placebo Lead-in Evaluation Phase: In the 2-week lead-in evaluation phase, subjects will receive placebo. They will undergo baseline symptom, medical, safety, and neurocognitive assessments. The subjects will undergo a physical examination; including neurological exam, an EKG; and laboratory tests of major organ functions (i.e., CBC, liver function tests, electrolytes, glucose, BUN/Creatinine, Urinalysis (UA), urine toxicology, and thyroid functions). Baseline antipsychotic levels will be collected. All women will have a pregnancy test, unless they are either surgically or hormonally post menopausal.

4-Week Double-Blind Treatment Phase: The study is a 4-week, placebo-controlled, double-blind study. Subjects will be randomized to either: MK-0777 GEM 3mg BID; MK-0777 GEM 8mg BID; or placebo. The unblinded site pharmacist will be notified of the treatment assignment, and will dispense study medication. Subjects will receive biweekly symptom assessments and weekly side effect and vital sign assessments. At week 4, subjects will undergo repeat administration of the neuropsychological test battery and the functional capacity and patient self-report of cognitive function measures. These assessments will be done over a two-day period. At week 5, subjects will also undergo a repeat slit lamp eye examination. We will also attempt to contact and schedule subjects who dropped out of the study prior to week 5 for the week 5 slit lamp eye examination. Finally, subjects will have blood samples collected for antipsychotic and MK-0777 levels at week 4.

6-Month and 12-Month Follow-up Evaluations: All subjects, regardless if they completed the 4-week double-blind treatment phase, will be contacted and scheduled for follow-up slit lamp eye examinations.

Randomization: Subjects will be randomly assigned to placebo or one of two doses of experimental treatment within strata defined by site.
**Medication Titration Schedule:** On week 1, day 1 - subjects randomized to MK-0777 GEM 3mg BID, will receive one 3 mg tablet and one placebo tablet in the morning and one 3 mg tablet and one placebo tablet in the evening.

On week 1, day 1 - subjects randomized to MK-0777 8 mg BID, will receive one 3 mg tablet and one placebo tablet in the morning and one 3 mg tablet and one placebo tablet in the evening. On week 1, day 3 - the dose will be increased to one 3 mg tablet and one placebo tablet in the morning and one 3 mg tablet and 5 mg tablet in the evening. On week 1, day 5 - the dose will be increased to one 3 mg tablet and one 5 mg tablet in the morning and one 3 mg tablet and 5 mg tablet in the evening.

Subjects who are randomized to placebo will get two placebo tablets in the morning and two in the evening.

Regardless of randomization assignment each subject will receive the same number of tablets per day (4). The MK-0777 3 mg, MK-0777 5 mg, and the placebo tablets will have the same identical appearance.

If subjects randomized to MK-0777 3mg BID are unable to tolerate the medication, then they will be instructed to skip the next scheduled dose of study medication. If the side effects dissipate, then they will be re-challenged with the original dose. If they are still unable to tolerate the original dose, then the non-blind pharmacist will reduce their dose to one 3 mg tablet and one placebo tablet. If subjects randomized to MK-0777 8 mg BID are unable to tolerate the medication, they will be instructed to skip the next scheduled dose of study medication. If their side effects subside, then they will be re-challenged on the higher dose. If still unable to tolerate the higher dose, then they will complete the study on the highest tolerated dose.

Each subject will receive their medications in four bottles: two in the morning and two in the evening, which will allow for specific dose reduction to occur and compliance checks to occur.

**4 Day Followup Phase:** After the end of week 4, subjects will be tapered off study medication according to the following schedule: in week 5, subjects who were randomized to MK-0777 GEM 3 mg BID, will take two placebo tablets in the morning and one 3 mg tablet and one placebo tablet at night for 4 days, then study meds will be discontinued; in week 5, subjects who were randomized to MK-0777 GEM 8 mg BID will take one 3 mg tablet and one placebo tablet in the morning and one 3 mg tablet and one 5 mg tablet in the evening for 1 day. Then they will take one 3 mg tablet and one placebo tablet in the morning and one 5 mg tablet and one placebo tablet in the evening for 1 day. Then they will take one 3 mg tablet and one placebo tablet in the morning and one 3 mg tablet and one placebo tablet in the evening for 1 day. Then they will take two tablets in the morning and one 3 mg tablet and one placebo tablet in the evening for 1 day. After week 5, day 4, study medication will be discontinued. Subjects who have been randomized to placebo will continue to receive two placebo tablets in the morning and two placebo tablets in the evening through week 5, day 4. At the end of the follow-up phase, subjects will have a neurological exam and laboratory tests of major organ functions (i.e., CBC, liver function tests, electrolytes, glucose, BUN/Creatinine, Urinalysis (UA), urine toxicology, and thyroid functions) as well as a side effects checklist and evaluation of vital signs.

**Maintenance of the Blind:** Study medication will be dispensed on a weekly basis. Subjects will be given three extra days of medication in case of a missed appointment. The blind will be broken only if a medical emergency requires this information. If this occurs, the subject
will be withdrawn from the study. All raters, investigators and other staff will be blind to treatment assignment except for the pharmacist. The pharmacist does not participate in assessing any of the primary symptom or side effect dependent variables and conveys no information about treatment assignment to subjects or staff except in a medical emergency.

**Compliance:** Subjects receiving 75% of their assigned medication will be considered compliant. The 75% criterion ensures that subjects will receive adequate treatment to evaluate the comparative efficacy of MK-0777 and placebo. Compliance will be monitored through bi-weekly pill counts and subject interviews. Study medications will be dispensed on a weekly basis and will only be dispensed after compliance is assessed and all assessments are completed. If a subject is observed to have a compliance problem, then this will be discussed with the subject and a plan formulated to bring the subject back within the compliance parameter. The plan may include contacting the subject's caretaker or scheduling increased clinic visits. These monitoring procedures have resulted in high levels of compliance. Compliance patterns will be carefully monitored in each treatment group and will be described as part of any presentation of study results.

Recruitment for potential subjects will be performed by reviewing subject records to determine eligibility based on the inclusion and exclusion criteria. Once qualifying records have been identified, potential subjects will be informed individually and/or in a group setting about the study. Those who express initial interest will be provided with additional information about the study, including the purpose of the study, a description of the procedures, and the overall length of the study. The length of the evaluation phase; the length of the double-blind study period; an explanation of double-blind and how it is determined; a list of the risks and side effects; expectations of the study participant, including all study tests and assessments; how to withdraw from the study; and what to do in case of a potential side effect will also be explained to potential subjects.

**Overdose Management:** In managing overdose with test medication, basic life support and CPR will be provided. Gastric lavage should be considered. Activated charcoal may be administered every 4 to 6 hours during the first 24 to 48 hours after ingestion. The possibility of multiple drug involvement will be considered. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation will be provided. If hypotension is present, standard medical practice will be used to manage the condition, including vasopressor therapy if indicated. The value of dialysis is unclear for MK-0777. The efficacy of flumazenil, a benzodiazepine antagonist, to treat MK-0777 overdose is unknown. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physician’s Desk Reference (PDR).

**DATA MANAGEMENT AND PROCEDURES**

**Design and Development**

This protocol will utilize a centralized data management center (CDMC), the Nathan Kline
Institute for Psychiatric Research. The CDMC will be responsible for development of the case report forms (CRFs), development and validation of the clinical study database, ensuring data integrity, and training clinical site and other protocol staff on applicable data management procedures and computerized systems. A web-based distributed data entry model will be implemented. This system will be developed to ensure that applicable guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld.

**Data Collection Forms**

Data will be collected at the study sites on paper CRFs. The CDMC will provide sites with a final set of standardized CRFs and CRF completion instructions. The CRFs will be distributed to the clinical sites by the CDMC. These forms are to be completed on an ongoing basis during the study. Forms should be completed according to the instructions provided and as discussed during training. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for tracking the completion of CRFs for each research participant. The investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

**Data Acquisition and Entry**

For paper CRFs, all CRFs must be completed legibly with black ballpoint pen. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. Corrections to paper CRFs must be initialed and dated by the person making the correction. Data entered into electronic CRFs shall only be performed by authorized individuals. Corrections to electronic CRFs shall be tracked electronically with time, date, individual making the change, and what was changed. Selected CRFs also require the investigators written signature or electronic signature, as appropriate. CRFs will be monitored for completeness, accuracy, legibility and attention to detail during the study. The investigator must retain a copy of all CRFs.

**Data Center Responsibilities**

The CDMC will 1) develop a data management plan and will conduct data management activities, 2) provide final CRFs for the collection of all data required by the study, 3) develop data dictionaries for each CRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from all participating clinical sites, 5) monitor any preliminary analysis data clean up activities, 6) rigorously monitor final study data clean up activities, (7) lock the study database and (8) provide the final, locked study database to designated organizations and personnel.

**Data Editing**

Completed forms/electronic data will be entered into the CDMC automated data acquisition and management system. On-line, real time data editing will be conducted. In addition, data will be edited each night for completeness and accuracy. If incomplete or inaccurate data are found, a data
clarification request will be forwarded to the clinical sites for a response. The clinical sites will resolve data inconsistencies and errors and enter all corrections and changes into the CDMC automated data acquisition and management system.

Data Transfer

The CDMC will transfer the final database to NIMH and other parties designated by NIMH, as requested, for storage and archive.

Documentation

Study documentation includes all case report forms, data correction forms, electronic data files, workbooks, source documents, monitoring logs, appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and signed patient consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, patient diaries, ultrasound photographs, patient progress notes, hospital charts, pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Training

The CDMC will provide comprehensive training on all data management procedures and computerized systems implemented for the study.

Sample Size and Data Analysis:

1. Primary Analysis:

The MATRICS battery consists of one or more tests to assess functioning in each of seven cognitive domains: speed of processing, attention/vigilance, working memory (verbal and nonverbal), verbal learning and memory, visual learning and memory, reasoning and problem solving and social cognition. The primary outcome for this trial will be the average of the z-scores for verbal and nonverbal working memory measures from the MATRICS battery, where z-scores are calculated using the mean and standard deviations of the normal sample in the MATRICS PASS study. Neurocognitive testing will be conducted at baseline and 4 weeks. Data reduction for analysis of neurocognitive testing will use these steps: i) individual neurocognitive test scores at baseline and follow-up will be converted to z-scores using the...
The analysis described below will be performed in each completed data set, and the analysis results combined, taking account of the between-imputation variability in estimates (Little and Rubin, 2002). These computations will be performed with the SAS7 procedures MI and MIANALYZE.

Treatments will be compared on average neurocognitive z-scores, using analysis of covariance, adjusting for baseline z-score. Treatment groups will be compared on an intent to treat basis, using all available follow-up data from each subject, analyzed according to their original treatment assignment.

The proposed study will use two-sided tests to compare two doses of active treatment to a single placebo control. The Holm-Bonferroni procedure (Holm, 1979) will be used to control Type I error while conducting multiple testing. The p-values from the two comparisons of active treatment versus control will be ordered from smallest to largest. If the smallest p-value is < 0.05/2, the corresponding null hypothesis of no difference will be rejected and the larger p-value will be compared to 0.05 to determine whether to reject the corresponding null hypothesis. If the smallest p-value is >0.05/2, no null hypotheses will be rejected.

2. Statistical power for primary analysis:

Sample size and statistical power for the ANCOVA analysis was calculated using the formula: \[ n = 2[z_\alpha + z_\beta]^2 \sigma^2 (1 - R^2) / d^2, \] where \( d = \) the difference in means, \( R \) is the within-subject correlation between the baseline and follow-up average z-scores, \( \sigma^2 \) is the cross-sectional variance of the scores at each time point, and \( z_\alpha \) and \( z_\beta \) are the percentiles of the normal distribution corresponding to the specified Type I error and power; e.g., for two-sided tests with Type I error = 0.05 and power = 0.80, \( z_\alpha = 1.96 \) and \( z_\beta = 0.842 \), respectively. The difference in change in scores divided by the cross-sectional standard deviation of the scores (\( d/\sigma \)) provides a convenient measure of the effect size of active treatment versus placebo. We may solve the power formula above to calculate the detectable effect size, \( d/\sigma = [2[z_\alpha + z_\beta]^2 (1 - R^2) / n]^{1/2} \). To correct for multiple comparisons (two dose levels of active treatment versus a placebo control), we would test the main outcome at two-sided alpha= 0.05/2. From preliminary studies of the
MATRICS battery, the ICC for the individual tests is somewhere between 0.6 and 0.8, suggesting that R for the overall z-score will fall within this range. If R=0.6, the detectable effect size will be 0.64; with R=0.8, the detectable effect size will be 0.48. Thus the planned study should have power to detect a large effect on neurocognitive outcomes, as well as providing preliminary effect size estimates for future, large N studies.

3. Secondary and Tertiary Analyses:

a. Other cognitive domains: The MATRICS battery of neurocognitive measures of seven cognitive domains: speed of processing, attention/vigilance, working memory (verbal and nonverbal), verbal learning and memory, visual learning and memory, reasoning and problem solving and social cognition. It is possible that improvements (or worsening) will be seen in other domains than working memory, as a secondary effect of working memory improvement or through drug action on other pathways. Accordingly, we will conduct secondary analyses to examine drug effects on a composite of non-working memory cognitive domains, calculated as follows: each measure will be converted into a z-score based upon the MATRICS PASS normative sample. For domains that have only one score, the domain score will be equal to the test score (e.g., the CPT d-prime average will also be the vigilance domain score). For domains that have more than one score, z-scores from each test in the domain will be averaged and then divided by the standard deviation of the mean domain score from the PASS normative sample. This calculation will derive a domain score that in the normative sample has a mean of 0 and a standard deviation of 1. This will allow direct comparisons for any patient sample to the MATRICS normative sample. The six non-working memory domain z-scores will then be averaged and divided by the normative composite standard deviation. This will create a composite score that will relate each individual’s performance to the normative sample. The non-WM average z-score will be analyzed with models similar to those specified for the WM z-score above.

To explore possible differences in the effects of treatments on specific cognitive domains, we will fit a mixed model for repeated measures, where cognitive domain is the repeated factor within the individual, using the model:

\[
\text{domain z-score} = \text{intercept} + \text{treatment} + \text{domain} + \text{treatment x domain}
\]

The treatment x domain interaction term in the model allows us to examine possible heterogeneity of effect size across cognitive domains.

As a secondary analysis, we will examine domain-specific differences in cognitive change between placebo and the two doses of active treatment. As a by-product of the model fitted for the primary analysis, we obtain adjusted (for baseline) end-point z-scores for each cognitive domain within each treatment group, together with a consistent estimate of the covariance of these estimated means. To take account of the multiple tests conducted (6 non-WM domains x 2 dose levels of active treatment compared to placebo = 14 comparisons), we will use Westfall’s (1997) multiple testing procedure, as implemented in the SAS macro %SIMTESTS (Westfall et al, 1999). In brief, Westfall’s procedure: i) uses simulations to obtain critical values for the pairwise comparisons, taking account of the correlation structure among the data and the contrasts specified; ii) takes account of logical constraints among the hypotheses.
tested in adjusting critical values at each step (e.g., if \( H_{12}: d_1=d_2 \) is rejected, then \( H_{13}: d_1=d_3 \) are and \( H_{23}: d_2=d_3 \) cannot both be true; hence, there are only two independent hypothesis tests for the three hypotheses \( H_{12}, H_{13}, H_{23} \); and iii) proceeds in a step up fashion, starting with comparing the minimum p-value among the set of initial set of pairwise contrasts to a critical value of \( \alpha = 0.05/K \), where \( K \) is the number of independent hypothesis test among the initial set of hypothesis, and then proceeding at each step to revise the critical value for testing according to the remaining number of independent hypothesis tests which have not yet been rejected. For large numbers of correlated comparisons, this procedure has significant power advantages over alternate step up closed testing procedures (e.g., Holm’s adaptation of the Bonferroni method) while maintaining strong control of Type I error rates at \( \alpha = 0.05 \).

Currently, procedures have not been developed for using the Westfall (1997) procedure with multiple imputed data sets. Accordingly, we will only plan to conduct these secondary analyses with the observed results for each domain. Should the Westfall procedure be extended to analysis of data sets completed by multiple imputation prior to the end of this study, we will use the extended procedure for the analysis of domain specific effects.

The presence of significant treatment effects will be considered very strong support for the experimental mechanism of action. In addition, if there appears to be enough of a cognitive effect to support further investigation of this class of agents, the study will also allow computation of effect sizes for each of the cognitive domains.

b. Effects of race/ethnicity and gender: We will repeat the primary analysis discussed above with added terms for race/ethnicity and male/female gender and their interactions with time and treatment, in order to explore whether sex or racial/ethnic differences may exist in neurocognitive effects of the study treatments.

c. Other outcome measures: Secondary analyses of other outcome measures will include:
   i. Proxy measures of functional capacity (UPSA)
   ii. Interview-based measures of cognition (SCoRS)
   iii. Symptom rating scales: BPRS total score and BPRS positive symptom score (items for Conceptual disorganization; Unusual thought content; Hallucinatory behavior; Suspiciousness), SANS total score and subscale scores for Affect; Alogia, asociality/Anhedonia; Avolition; Calgary Depression Scale total score, and CGI score.
   iv. Ratings of potential side effects of treatment include: Simpson-Angus Scale (SAS) total score; Barnes Akathisia Scale (BAS) total score; Abnormal Involuntary Movement Scale (AIMS) total score, evidence of new onset or worsened cataracts or uveitis at 4 weeks and 6 months, and a side effect checklist.

   All exploratory tests for treatment effects on these other outcome measures will be conducted at two-sided \( \alpha = 0.05 \), using the Holm-Bonferroni procedure to control for multiple comparisons between groups, but not adjusting for multiplicity of outcome measures. Ratings on the first two categories of outcome measure will be analyzed using ANCOVA models adjusting for baseline score. Repeated symptom ratings will be analyzed using a mixed model for repeated measures to look for difference in (linear) trend in symptom rating scores versus time, using the model score = intercept + treatment + time + treatment x time, where the treatment x time interaction tests for differences between placebo and the two doses of active
treatment time trends in symptom scores.

Extrapyramidal side effect (EPS) ratings on the SAS, BAS and AIMS total scores will be analyzed using pairwise comparisons of dose groups to placebo, using a rank test for differences in the correlation between EPS score and study visit, which is suitable for detecting presence of adverse trends in vulnerable subgroups, and more suited to non-normally distributed EPS data (McMahon et al, 2005). The twenty-two side effects specified on a side effects checklist are rated biweekly during double blind treatment as 1=Anone®, 2=Amild®, 3=Amoderate® or 4=Asevere®. To summarize this rating data, the most severe rating of each side effect for each subject during follow-up will be determined. The treatments will then be compared on worst ranking using a Mantel-Haenszel chi-square statistic for ordinal data. Presence of new onset or worsened cataracts at 4 weeks and 1 year (if any) will be compared among treatments using Fisher’s exact test.

It should be noted that the eligibility criteria restrict study participation to subjects with limited positive symptoms and extrapyramidal symptoms, so that it may be unlikely that such a large response in these areas will be observed such a response in this trial. Analysis of effects on these symptoms will be conducted mainly with the goal of identifying any potential for symptom worsening, or of unexpectedly strong symptom remission, which might confound interpretation of cognitive changes.

The primary outcome measures for SSAEP are oscillatory evoked potential spectral power on the alpha, beta, and gamma range. The primary outcome measure is MMN to stimulus deviance. Data will be analyzed using repeated measure ANOVA with within subject factor of treatment.

Potential Risks/Discomforts:

The major risks of participation in this study are those associated with the study drug: MK-0777. In preclinical toxicology studies, MK-0777 was associated with the development of lenticular opacities (cataracts). In 2-year studies, treatment-related posterior subcapsular cataracts were observed in female rats at week 105 (dose: 300 mg/kg/day), and treatment-related anterior subcapsular cataracts were observed in female mice at week 100 (dose: 1000 mg/kg/day). In a 53-week dog study, cataracts were observed at 10 and 30 mg/kg/day. In a 14-week oral toxicity study, 6/7 beagle dogs developed cataracts by week 12 (dose: 100 mg/kg/day). In a 53-week oral toxicity study, with an interim 27-week evaluation, treatment-related cataracts were first found at week 26 on 30 mg/kg/day and at week 52 on 10 mg/kg/day. No treatment-related cataracts were observed on the 3 mg/kg/day dose. The drug exposure observed with the 10 mg/kg/day is 21 fold greater than the expected exposure with the maximum dose proposed in the current protocol. In Merck studies 019, 020, 022 and 026, 15 of the 80 subjects exposed to the study drug had post-study ophthalmological examinations. Five of 15 subjects were observed to have cataracts. Three of the subjects had a known history of cataracts prior to participation in one of these studies. In addition, none of these three subjects had posterior subcapsular cataracts, which are the type of cataracts that could potentially be related to study drug. The other two subjects had no pre-existing history of cataracts. They both were observed to have posterior subcapsular cataracts and they received the study drug, 8 mg BID, for 4 weeks, which suggests that the risk for developing cataracts is related to the dose of drug and the duration of exposure to the drug. This dose is the highest dose that we will be using in our
proposed study and also represents the maximum length of exposure. Neither of these patients had a pre-study slit lamp examination. The post-study examination was 10 – 12 months after their last exposure to the study drug, which introduces the possibility of intervening factors causing the observed cataracts. We will be using both 3 mg BID and 8mg BID doses in our study. In clinical studies conducted to date, the most frequent side effects were: constipation; dry mouth; flatulence; nausea; increased appetite; dizziness; disturbance in coordination; and insomnia (see Investigator Brochure). There have been no reported changes in pulse or respiratory rate or blood pressure elevations. There have been no deleterious effects on QRS or QTc intervals. There have been no deleterious effects on clinical laboratory tests.

We will be using both 3 mg BID and 8mg BID doses in our study. In clinical studies conducted to date, the most frequent side effects were: constipation; dry mouth; flatulence; nausea; increased appetite; dizziness; disturbance in coordination; and insomnia (see Investigator Brochure). There have been no reported changes in pulse or respiratory rate or blood pressure elevations. There have been no deleterious effects on QRS or QTc intervals. There have been no deleterious effects on clinical laboratory tests.

General clinical procedures utilized to ensure against or minimize potential risks associated with MK-0777 treatment include a pre-investigation medical history, physical examination, including neurological exam, EKG, and clinical laboratory tests. Side effect and vital sign assessments will be conducted weekly throughout the course of the study. A subject who reports or exhibits symptoms of uveitis will undergo an eye exam by the opthamologist who examined the subject prior to study entry. If uveitis, with 1+ or worse flare or cells is present, the subject will be treated for the uveitis and removed from the study. A pregnancy test will be performed for women who are not surgically or hormonally post menopausal prior to study entrance and pregnant women will be excluded from the study. Specific clinical procedures will include baseline, end-of-study, 6-month and 12-month slit-lamp examinations. The baseline examination will be conducted to exclude subjects with uveitis as evidenced by 1+ or greater flare or cells or posterior subcapsular cataracts with a LOCS III grade of 1.0 or higher. Slit-lamp eye exams for each subject will be done by the same opthamologist, in order to more accurately diagnose any changes in the eye. The end-of-study, 6-month and 12-month examinations will be conducted to monitor subjects for potential immediate and long-term development of cataracts. In order to minimize side effects with the higher dose of MK-0777, subjects randomized to MK-0777 GEM 8 mg BID will have their dose titrated to the target dose over a one week period. There is also the possibility that MK-0777 may have unexpected effects on patients with schizophrenia and may lead to a worsening of their positive symptoms. In response to the possibility that MK-0777 may exacerbate positive symptoms, we will assess the presence and severity of positive symptoms and depression at weeks 2 and 4 of the double-blind phase using the BPRS and CDRS. In addition, we provide 24-hour/7-day on call coverage for all outpatient subjects.

The clinical and neuropsychological tests are non-invasive clinical assessments with minimal risk. There is the possibility that the subject will find the evaluations stressful. The likelihood of this occurring is not very significant. However, frequent breaks in the testing will be allowed to insure that the subject does not become over stressed.

The brain wave procedures are non-invasive clinical assessments with minimal risk. Some people may have skin irritation and redness from the electrodes and/or the paste used for electrodes, which usually disappears in a day or so. Occasionally some people may experience a headache caused from wearing a tight cap with the electrodes. We will adjust the tightness of the electrodes cap placed on your head or remove the electrodes if this occurs. All these tests are done in a dimly lighted room. This may cause inconvenience and discomfort. If participants feel the strain is becoming too much, they are encouraged to ask for a break at any time.

All personnel have completed required education programs in the protection of human research participants. In addition, all Key Personnel have completed the NIH required education
programs.

To minimize risks associated with clinical assessments, research assistants and therapists, trained to detect any untoward effects, will administer the clinical assessments and neuropsychological tests. In addition, if necessary, then frequent breaks will be allowed during the neuropsychological testing sessions to minimize any possible stress.

The NIMH Data and Safety Monitoring Board will monitor the occurrence of side effects and adverse events. A serious adverse event (SAE) is any adverse experience that is unexpected or: a) results in death; b) results in persistent or significant disability/incapacity; c) results in or prolongs an existing inpatient hospitalization (even if the hospitalization is a precautionary measure for observation); d) is a congenital anomaly/birth defect in offspring of subjects taking the product regardless of time to diagnosis.

In addition to the monitoring and reporting of the above adverse events, study participants will be withdrawn from the protocol if any of the following criteria are met.

1) Objective Evidence for Clinical worsening, as indicated by the following:
   a) The subject is judged to be entering an exacerbation of his/her illness by the treating clinician and any one of the following:
      i. relative to the baseline BPRS; an increase of 3 points or more on any one of the following BPRS items: somatic concern, conceptual disorganization, hostility, suspiciousness, hallucinatory behavior, and unusual thought content;
      ii. an increase of 2 or more on the CGI global severity item or
      iii. complete cessation of eating and drinking for period exceeding 24 hours.

2) Pregnancy

   From the standpoint of privacy and confidentiality, the subject's welfare will be safeguarded by responsible, systematically controlled procedures for the collection of information for both clinical and research purposes. MPRC and TURNS investigators, the University of Maryland School of Medicine IRB and other TURNS IRBs, the NIH Data and Safety Monitoring Board, and the Federal Drug Administration will have access to the research files. Also, the subject's agreement to release information will be required for requests for information to and from other agencies. Recorded information for research purposes, including computer input data, will be identified by code number rather than by name, and subsequent published or presented material related to the project will not be traceable to specific individuals.

Following completion of data collection, patient files will be maintained in a secure area in retrievable form for future patient-requested clinical use.

**Potential Benefits:**

There is no guarantee that a participant will receive direct benefit from this study. However, possible benefits of participating in this research may include improvement of one's condition and relief of symptoms. Also, a subject's condition may be monitored more closely than usual. In addition, new information may be learned that would be helpful in developing new therapies for other people with similar illnesses. It is possible however, that no therapeutic or other direct benefits will result during or following completion of this study.

**Risk/Benefit Ratio:**
The major risks of the study are associated with MK-0777 treatment. MK-0777 and benzodiazepines have been shown to be relatively safe when administered to patients with schizophrenia. Previous MK-0777 studies in subjects with Generalized Anxiety Disorder suggest that the drug is well tolerated. The age of the subjects in these studies is comparable to the age range in the current proposed study. The symptom ratings, cognitive and neuropsychological assessments, and blood draws are associated with minor risks only. The potential for developing a drug that treats abnormalities in cognition in schizophrenia outweighs the mild to moderate risks of uncomfortable side effects.

Consent Procedures:

All subjects will be provided a complete description of the proposed study, including the purpose of the study, procedures, risks, and alternatives to participation. Should the subject express interest in participation, personnel trained in the informed consent process (see listed personnel) will review the Informed Consent document with the subject, and the subject will be given a copy of the form for further study. A non-investigator clinician member of the treatment team will assess whether the prospective participant is able to participate in the informed consent process (the Evaluation to Sign Consent Form). If the subject is able to participate in the informed consent process and agrees to participate in the study, then agreement to participate will be documented on the Informed Consent form. If the subject is not able to participate in the informed consent process, then they will not be entered into the study.

Access to Research Data:

MPRC and TURNS research staff and data management team will have access to this data. Merck will have access to coded data.

Subject Payment:

Participants will receive $15 for each week of study participation. Pay forms are filled out upon study completion.

Study Drug and IND:

MK-0777 (C_{20}H_{22}N_{7}OF)

MK-0777 is an experimental drug. MK-0777 is the only experimental drug that will be used in the current study. MK-0777 does not induce nor inhibit P450 isoenzymes. MK-0777 is primarily metabolized by P450 isoenzyme 3A4. Therefore, there should not be any significant interactions between MK-0777 and antipsychotic medications. The IND# 76,914. The drug will be provided by Merck and Co., Inc. The drug will be stored in the MPRC Outpatient Research Program pharmacy. The MPRC Outpatient Research Program pharmacist, Dr. Verovsky, will be responsible for the accountability, labeling, dispensing, and storage of the drug. The study subjects will self-administer the drug by mouth.
References:

Akbarian S, Kim JJ, Potkin SG, Hagman JO, Tafazzoli A, Bunney Jr WE, and Jones EG. 1995. Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. Arch Gen Psychiatry 52:258-266.


McMahon RP, Arndt S, Conley RR. 2005. More powerful two-sample tests for differences in repeated measures of adverse effects in psychiatric trials when only some patients may be at risk. Statistics in Medicine, 24:11-21.


