A Randomized Clinical Trial of MK-0777 for the Treatment of Cognitive Impairments in People with Schizophrenia


Background: In a previous pilot study, MK-0777—a γ-aminobutyric acid (GABA)\(_{A}\) α2/α3 partial agonist—was reported to improve delayed memory and cognitive measures of prefrontal cortical function in people with schizophrenia. The current study was designed to further examine the efficacy and safety of MK-0777 for the treatment of cognitive impairments in schizophrenia.

Methods: Sixty people with DSM-IV schizophrenia entered a 4-week, multi-center, double-blind, placebo-controlled, randomized clinical trial. Participants were randomized to: MK-0777 3 mg b.i.d. (n = 18); MK-0777 8 mg b.i.d. (n = 21); or placebo (n = 21). Participants were clinically stable. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery, AX-Continuous Performance Test, and N-Back were used to assess cognition. The University of California San Diego (UCSD) Performance Based Skills Assessment-2 and the Schizophrenia Cognition Rating Scale assessed functional capacity and served as functional outcome coprimary measures.

Results: There were no significant group differences on the primary outcome measure, the MATRICS Consensus Cognitive Battery composite score. Secondary analyses suggested that participants randomized to placebo performed significantly better on visual memory and reasoning/problem-solving tests than participants assigned to either MK-0777 dose. There were no significant group differences on the AX-Continuous Performance Test or N-Back d prime scores or UCSD Performance-Based Skills Assessment-2 and Schizophrenia Cognition Rating Scale total scores. In general, MK-0777 was well-tolerated with minimal side effects.

Conclusions: The study results suggest that MK-0777 has little benefit for cognitive impairments in people with schizophrenia. The GABA\(_{A}\) receptor remains a promising target, but a more potent partial agonist with greater intrinsic activity at the GABA\(_{A}\) α2 site might be needed for cognitive enhancement in schizophrenia.

Key Words: Clinical trial, cognition, functional capacity, γ-aminobutyric acid, schizophrenia, symptoms

People with schizophrenia have a broad range of neurocognitive impairments, including abnormalities in attention, executive function, visual and verbal learning and memory, working memory, processing speed, and social cognition. These impairments are major determinants of functional outcome in schizophrenia (2,3). First- and second-generation antipsychotics have limited benefits for these impairments (4). The use of add-on pharmacological agents might offer a viable approach for the treatment of these impairments, because they can be used to modulate specific neurotransmitter systems hypothesized to be involved in the pharmacology of cognitive functions.

γ-aminobutyric acid (GABA) is the major central nervous system inhibitory neurotransmitter. GABAergic mechanisms are important for regulation of prefrontal cortical function, through their modulation of glutamatergic pyramidal cells (5). In particular, the GABAergic chandelier cell type interneuron inhibits pyramidal neuron output through activation of GABA receptors containing the α2 subunit located on the axon initial segment, a mechanism thought to support the development and maintenance of recurrent activity necessary for intact prefrontal function (5).

Postmortem studies have found decreased levels of glutamic acid decarboxylase (GAD)\(_{67}\) messenger RNA expression in the prefrontal cortex (6–9). The GAD\(_{67}\) reduction seems to be restricted to those cells that contain the calcium-binding protein parvalbumin, which includes chandelier cell interneurons (7,10). In people with schizophrenia with decreased GAD\(_{67}\), there is also a decrease in GABA reuptake transporter messenger RNA levels (11); the density of chandelier cell connections with the pyramidal cell axon initial segment (12,13); and immunoreactivity of the GABA plasma membrane transporter-1 in chandelier cell axon terminals (12). Finally, there seems to be a marked increase in GABA\(_{A}\) α2 subunit density on the axon initial segment (14).
These postmortem results are consistent with a marked decrease in GABAergic inhibition of dorsolateral prefrontal cortex pyramidal cell glutamatergic transmission, which could have important implications for our understanding of cognitive impairments in schizophrenia (5). Specifically, intact GABAergic function has been shown to be required for normal working memory (15–18). People with schizophrenia have been shown to have verbal and visual working memory impairments (1,19–24). Working memory might also be critical for a number of other cognitive processes, so that improvement of working memory function could lead to improvement in other cognitive domains. Agents that increase GABA inhibition of cortical pyramidal cells would be hypothesized to improve working memory and possibly other cognitive impairments.

MK-0777 is a GABA_A_α2/α3 partial agonist, with approximately 10%–20% of the potency of a full GABA_A_α2 agonist. MK-0777 is functionally selective for the α2 and α3 subunits, with virtually no activity for the α1 and α5 subunits (25,26). Therefore, it is hypothesized to cause less sedation than benzodiazepines (27). In animal studies, MK-0777 was observed to cause less sedation than benzodiazepines (25,26). In a previous pilot study, MK-0777 improved delayed memory performance and decreased reaction time on selected measures of prefrontal cortical function (28).

The purpose of the current study was to conduct a larger scale trial to examine the efficacy and safety of two doses of MK-0777, 3 mg b.i.d. and 8 mg b.i.d., in the treatment of cognitive impairments in people with schizophrenia.

**Methods and Materials**

The National Institute of Mental Health Treatment Units for Research on Neurocognition in Schizophrenia Network implemented the 4-week, placebo-controlled, parallel group, double-blind study. Inpatients or outpatients 18–60 years of age, who met DSM-IV-TR criteria for schizophrenia, were selected for study entry. Participants were diagnosed on the basis of information from the Structured Clinical Interview for DSM-IV (29), direct assessment, family informants, and past medical records. Participants were required to be clinically stable and in the nonacute phase of their illness and to meet the following inclusion criteria (30): 1) treatment with one second-generation antipsychotic medication other than clozapine for the previous 2 months, with no dose change in the month before study entry; 2) Brief Psychiatric Rating Scale (BPRS) (31) hallucinatory behavior and unusual thought content item scores ≤ 4; 3) BPRS conceptual disorganization item ≤ 4; 4) Simpson-Angus Scale (SAS) (32) total score ≤ 6; and 5) Calgary Depression Scale (CDS) (33) total score ≤ 10 (33,34). To facilitate recruitment, the aforementioned criteria were amended halfway through the study to allow treatment with no more than two second-generation antipsychotic medications other than clozapine, and the cut-off score for BPRS hallucinatory behavior and unusual thought content items was changed to ≤ 5.

Participants were required to validly complete the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (35,36) (i.e., the neuropsychological tester and the site neuropsychologist judged their performance to reliably reflect their ability on those aspects of cognition that the test was intended to measure). To minimize potential ceiling effects, participants were required to score at least 1 SD below maximum on one or more of the following tests: Letter-Number Span; Hopkins Verbal Learning Test; and Identical Pairs Continuous Performance Test (CPT). Finally, participants were required to have a Wechsler Test of Adult Reading (37) raw score ≥ 6.

Participants were excluded if they had a DSM-IV diagnosis of alcohol or substance abuse (other than nicotine) within the last month, alcohol or substance dependence (other than nicotine) within the last 6 months, or mental retardation; had a history of significant head injury/trauma or clinically significant medical or neurological disease; were treated with drugs known to act at the GABA_A receptor or to inhibit CYP3A4; had a history of severe benzodiazepine withdrawal; or participated in a clinical trial of investigational medication within 60 days. Women of childbearing age were included if using adequate birth control.

The institutional review boards approved the study protocol and informed consent procedures. Written informed consent was obtained from all participants after study procedures had been fully explained and before study participation. Participant ability to provide valid informed consent was documented with study specific procedures.

**Assessments**

The MCCB was used to assess neuropsychological test performance. The MCCB comprises 10 tests, which assess seven cognitive domains (35). The MCCB composite score is a standardized mean of the seven domain scores. The T scores are standardized to normative data and have an estimated mean of 50 and SD of 10 in the general healthy population (36).

In addition, because of their previous use to evaluate cognitive effects with this compound (28), the AX-CPT (38) and the N-Back (39) were used to assess prefrontal cortical cognitive function. The AX-CPT is a modification of the traditional CPT, in which AX trial frequency is increased to 70%. The increased AX trial frequency requires greater use of context to overcome the induced propensity to respond to the “X” probe on trials that do not contain the “A” cue (40). The N-Back is a sequential letter working memory task, which varies working memory load by requiring the participant to identify whether the test stimulus is identical to the immediately preceding letter (0-back) or the letter presented 1 trial back (1-back) or two trials back (2-back) (39).

A modified version of the University of California San Diego (UCSD) Performance-Based Skills Assessment (UPSA) (40), the UPSA-2, was used to assess functional capacity. The UPSA-2 contains a sixth component: Medication Management, and the content complexity and number of items required to be remembered were increased for the Comprehension/Planning, Financial Skills, and Transportation components to reduce potential for ceiling effects. The Schizophrenia Cognition Rating Scale (SCoRS) (41) is an interview-based measure used to assess cognition. The MCCB, UPSA-2, SCoRS, AX-CPT, and N-back were obtained at Evaluation Week 1 and Treatment Phase Week 4.

The BPRS positive symptom item total score was used to assess positive symptom change. The BPRS positive symptom items are conceptual disorganization, hallucinatory behavior, unusual thought content, and suspiciousness. The modified Scale for the Assessment of Negative Symptoms (SANS) (42) total score was used to assess negative symptom change. The CDS was used to assess depressive symptom change. The Clinical Global Impression severity of illness item (CGI-S) was used to assess global changes. The BPRS, SANS, CDS, and CGI-S were obtained at Screening, Evaluation Phase Week 2, and biweekly during the Treatment Phase.

The MCCB and UPSA raters were trained on the administration and scoring of these instruments with video and group training sessions and were individually certified by an expert on these assessments. The SCoRS raters were trained in a group education format, in which they viewed and scored a series of videotapes. Symptom raters were required to be reliable on the BPRS and SANS.
(intraclass correlation \( \geq .80 \)). Quarterly reliability meetings were conducted throughout the study to ensure that the raters maintained the intersite intraclass correlation criterion of \( \geq .80 \). All raters were blind to treatment assignment.

**Safety Assessments**

The SAS (32) and Abnormal Involuntary Movement Scale (AIMS) (43) were used to assess abnormal motor movements. The SAS and AIMS were administered at Screening, Evaluation Phase Week 2, and biweekly during the Treatment Phase.

A standard chemistry panel, complete blood count, urinalysis and urine toxicity screen, and electrocardiogram were obtained at Screening and at the end of the Treatment Phase. The Side Effect Checklist (SEC) was used to assess side effects and monitor vital signs. The SEC comprises 22 common side effects, which are rated from 1 (none) to 4 (severe). The SEC and vital sign ratings were conducted at Evaluation Phase Weeks 1 and 2 and weekly during the Treatment Phase.

**Study Design**

Participants who met inclusion criteria entered a 2-week Evaluation Phase during which they underwent baseline cognitive, symptom, and safety assessments. Participants who continued to meet inclusion criteria entered the 4-week, double-blind Treatment Phase and were randomized to MK-0777 3 mg b.i.d.; MK-0777 8 mg b.i.d.; or placebo b.i.d. Participants randomized to MK-0777 8 mg b.i.d. were started on 3 mg b.i.d., and their dose was titrated over the first week to the target dose. Participants randomized to MK-0777 3 mg b.i.d. were started on this dose. The MK-0777 \( T \), is approximately 7 hours and the \( T_{max} \) is 6–7 hours; therefore we used a twice daily dosing schedule.

If side effects interfered with the tolerability of the study medication, the participant was instructed to skip a dose and then resume treatment with the prescribed dose. If still unable to tolerate the study medication, then the dose could be lowered to alleviate side effects. The side effects most likely to affect MK-0777 tolerability were dizziness, incoordination, and sedation. At the end of the Treatment Phase, all participants were tapered off their study medication to minimize potential withdrawal effects.

The study biostatistician established computer-generated randomization sequences for each site. Randomization was performed with the permuted block method, randomly drawing from 3 or 6 size blocks, to limit imbalance in numbers between groups. Until the trial was concluded, the randomization sequence was only available to the biostatistician and to an unblinded pharmacist at each site, whose only role was to dispense medication. In response to a randomization request, the biostatistician sent a code number to the unblinded pharmacist, which identified the next treatment to be dispensed from the treatment sequence. Randomization was stratified by site.

Medication compliance was assessed by weekly pill count. All participants who received 75% or more of their assigned study medication were considered compliant.

**Statistical Analyses**

The sample size was determined with the analysis of covariance (ANCOVA) power formula, \( n = 2(z_{0.025} + z_{\alpha})^2 s^2 (1 - R^2)/d^2 \), with \( z_{0.025} = 2.24, z_{\alpha} = .842 \) (corresponding to power = .80), \( R \) is the correlation between baseline and end of study measures of the primary outcome (estimated to equal .6 for the MCCB composite score), \( d \) the difference between groups, and \( s \) the SD of the primary outcome.

We planned to enroll 30 participants/group, which would have enabled us to detect an effect size = .73 with power = .80. The actual recruitment was only approximately 20 participants/group, but the observed \( R \) approximately = .9, suggesting power to detect an effect size of .49.

An ANCOVA, adjusting for baseline scores, was used to compare treatment groups on cognitive and functional measures. The pre-defined primary cognition outcome measure was the MCCB composite \( T \) score, tested at overall two-sided \( \alpha = .05 \). The pre-defined primary functional outcome measure was the UPSA summary score. Exploratory analysis of variation in treatment effects among the different MCCB measures was performed with the mixed model for repeated measures ANCOVA: Week 4 \( T \)-score = baseline \( T \) score + measure + treatment + treatment \( \times \) measure, where measure was a categorical variable indicating the different MCCB tests, and the treatment \( \times \) measure effect tested whether the treatment effect differed significantly among the various tests.

The AX-CPT and N-back accuracy results were summarized with the d-prime statistic (44). For the AX-CPT, only BX trials were used to calculate the false alarm rate. For the N-back, trials with novel and repeated distractors were pooled in calculating the false alarm rate. The N-back response times (RTs) were analyzed with the ANCOVA model \( \log(\text{RT}) = \text{baseline log(\text{RT})} + \text{response type} + \text{treatment} + \text{treatment} \times \text{response type} \), where response type distinguishes target, repeat nontarget, and novel nontarget trials.

Symptom data were analyzed with a mixed model for unbalanced repeated measures ANCOVA, with data from all participants who completed at least one symptom assessment to fit the model: follow-up score = baseline score + treatment + week + treatment \( \times \) week, where the treatment effect tests the average difference across weeks between treatment groups, and the treatment \( \times \) week interaction assesses whether this difference varies between Weeks 2 and 4. Mixed models were fitted with SAS PROC MIXED (SAS, Cary, North Carolina), with the Kenward-Rogers method to estimate degrees of freedom. The treatment \( \times \) week interaction was nonsignificant for all variables assessed, and only average difference tests and estimates are reported.

Group differences on SAS and AIMS total scores were examined by calculating the \( \tau-b \) rank correlation between score and week for each participant and comparing the distribution of these trend scores with the Conover-Salsburg rank test (45,46). Fisher exact test was used to compare treatments on the number of participants who, at any point during follow-up, had new or worsened (compared with baseline) side effect severity. The effects of treatment on laboratory assays were tested with ANCOVA, whereas the effects of treatment on vital signs were tested with mixed model ANCOVA.

**Results**

The study was conducted between July 2007 and June 2009. Sixty-four participants were randomized: 19 were randomized to MK-0777 3 mg b.i.d.; 22 were randomized to MK-0777 8 mg b.i.d.; and 23 were randomized to placebo (see Figure 51 in Supplement 1 for participant flow details). Fifty-three participants completed the study: MK-0777 3 mg b.i.d.: \( n = 18 \); MK-0777 8 mg b.i.d.: \( n = 18 \); placebo: \( n = 17 \). Three participants dropped out before receiving study drug (one randomized to each group), and one participant dropped out before any postrandomization ratings (randomized to placebo). These participants were not included in either efficacy or safety analyses. The demographic and baseline clinical characteristics of participants included in either analysis are presented in Table 1.

**MCCB**

There were no overall significant group differences on MCCB composite score change \((F(2,49) = 1.61; \ p = .21)\) (Table 2). In
Table 1. Demographic Data and Baseline Clinical Characteristics

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Table 2. MCCB Composite and Individual Test T Scores

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Table 3. ANCOVA for change in AX-CPT performance

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<td>2.46</td>
<td>.492</td>
</tr>
<tr>
<td></td>
<td>.39</td>
<td>2.47</td>
<td>.679</td>
</tr>
<tr>
<td></td>
<td>.09</td>
<td>2.46</td>
<td>.917</td>
</tr>
<tr>
<td></td>
<td>3.18</td>
<td>2.46</td>
<td>.051</td>
</tr>
<tr>
<td></td>
<td>1.44</td>
<td>2.47</td>
<td>.248</td>
</tr>
<tr>
<td></td>
<td>.40</td>
<td>2.47</td>
<td>.671</td>
</tr>
<tr>
<td></td>
<td>.377</td>
<td>2.46</td>
<td>.030</td>
</tr>
<tr>
<td></td>
<td>.20</td>
<td>2.46</td>
<td>.841</td>
</tr>
<tr>
<td></td>
<td>1.88</td>
<td>2.45</td>
<td>.163</td>
</tr>
</tbody>
</table>

Note: Values are mean (± SD); there was no significant variation in the magnitude of treatment differences among the cognitive measures [F(18) = .73, p = .76]. MCCB, MATRICS Consensus Cognitive Battery; ANCOVA, analysis of covariance; CPT-IP, Identical Pairs Continuous Performance Test; BACS, Brief Assessment of Cognition in Schizophrenia; BMVT-R, Brief Visuospatial Memory Test–Revised; HVLT-R, Hopkins Verbal Learning Test–Revised; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test; NAB, Neuropsychological Assessment Battery; WMS, Wechsler Memory Scale; LNS, Letter-Number Span.

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Table 3. N-Back and AX-CPT d-Prime Scores

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo</th>
<th>MK-0777, 3 mg b.i.d.</th>
<th>MK-0777, 8 mg b.i.d.</th>
<th>ANCOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 4</td>
<td>Week 0</td>
<td>Week 4</td>
</tr>
<tr>
<td>N-Back</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 17)</td>
<td>(n = 17)</td>
<td>(n = 16)</td>
<td>(n = 16)</td>
<td>(n = 17)</td>
</tr>
<tr>
<td>0-Back</td>
<td>3.7 (0.5)</td>
<td>3.7 (0.6)</td>
<td>3.7 (0.6)</td>
<td>3.7 (0.6)</td>
</tr>
<tr>
<td>1-Back</td>
<td>2.7 (0.8)</td>
<td>2.8 (0.8)</td>
<td>3.0 (0.6)</td>
<td>3.0 (0.7)</td>
</tr>
<tr>
<td>2-Back</td>
<td>1.4 (0.8)</td>
<td>1.6 (0.6)</td>
<td>1.4 (0.6)</td>
<td>1.4 (0.6)</td>
</tr>
<tr>
<td>AX-CPT</td>
<td>(n = 16)</td>
<td>(n = 16)</td>
<td>(n = 16)</td>
<td>(n = 16)</td>
</tr>
<tr>
<td>d-Prime</td>
<td>2.4 (1.1)</td>
<td>2.2 (1.4)</td>
<td>2.5 (1.1)</td>
<td>2.5 (1.2)</td>
</tr>
</tbody>
</table>

Values are mean (±SD). ANCOVA, analysis of covariance.

Discussion

The study results suggest that MK-0777 does not significantly improve cognitive impairments in people with schizophrenia. There were no significant differences between the two MK-0777 treatment arms and placebo on the MCCB composite score. In secondary analyses, participants randomized to placebo compared with those randomized to MK-0777 8 mg b.i.d. exhibited greater improvement on the Brief Visual Memory Test-Revised and the Neuropsychological Assessment Battery mazes tests. However, neither of these two group differences would have been significant after correcting for multiple comparisons. There were no significant group differences on the two ancillary cognitive measures, the N-back and AX-CPT, or on the two functional measures, the UPSA summary score or the SCORs interviewer global rating score. The overall ANCOVA test for treatment effects on the SCORs Interview Global rating was nonsignificant (placebo: Week 0: 3.8 ± 2.3, and Week 4: 3.6 ± 1.8; MK-077 3 mg b.i.d.: Week 0: 4.8 ± 2.3, and Week 4: 4.6 ± 2.1; MK-077 8 mg b.i.d.: Week 0: 4.1 ± 2.3, and Week 4: 4.0 ± 2.4; F(2,47) = .17; p = .84). There were also no significant treatment differences on the participant, informant, and interviewer change rating scores (all F values < .50, and all p values > .30) (Table S4 in Supplement 1).
Table 6. AIMS and SAS Total Scores

<table>
<thead>
<tr>
<th>Measure</th>
<th>Week</th>
<th>Placebo</th>
<th>MK-0777, 3 mg b.i.d.</th>
<th>MK-0777, 8 mg b.i.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIMS Total Score</td>
<td>0</td>
<td>.6 (2.0)</td>
<td>.2 (3.3)</td>
<td>.9 (1.5)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>.3 (6)</td>
<td>.2 (4.4)</td>
<td>1.0 (2.0)</td>
</tr>
<tr>
<td>SAS Total Score</td>
<td>0</td>
<td>1.1 (1.5)</td>
<td>.8 (1.2)</td>
<td>1.4 (1.6)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.2 (1.3)</td>
<td>.7 (1.0)</td>
<td>1.2 (1.5)</td>
</tr>
</tbody>
</table>

Abnormal Involuntary Movement Scale (AIMS) total score: placebo vs. MK-0777 3 mg b.i.d., F(1,37) = 0.19, p = .66; placebo vs. MK-0777 8 mg b.i.d., F(1,37) = 0.52, p = .22. Simpson-Angus Scale (SAS) total score: placebo vs. MK-0777 3 mg b.i.d., F(1,34) = 0.65, p = .43; placebo vs. MK-0777 8 mg b.i.d., F(1,36) = 0.01, p = .91.

only observed group difference in the UPSA component measures favored the placebo group.

MK-0777 did not exhibit any significant benefits for BPRS total or positive symptom item scores, SANS total score, or CDS total score. In participants randomized to MK-0777 3 mg b.i.d. there was a small but significant worsening on the CGI-S score. Both doses of MK-0777 were well-tolerated with minimal side effects.

The present results stand in contrast to those from the previous MK-0777 study. In particular, Lewis et al. (28) found a significant group difference on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (47) delayed memory index; whereas, in the current study, there were no significant group differences that favored MK-0777 on any of the MCCB test measures. In addition, Lewis et al. (28) reported a significant group difference in the combined N-back and Preparing to Overcome Prepotency Task (POP) reaction time measure; there were no other significant group differences on the AX-CPT, N-Back, and POP ancillary measures. In the current study, there were no significant performance or reaction time differences with either the AX-CPT or N-back ancillary measures. There are several possible explanations for these differences between the two studies. The most important of which is the small sample size of the Lewis et al. study, which limits the reliability of their estimate of subject test performance and experimental drug effects. Second, although Lewis et al. found a significant benefit for MK-0777 for the RBANS delayed memory index, other RBANS measures, including the visuospatial constructional and attention indexes, showed a numerically larger if not statistically significant advantage for placebo, which suggests that the limited benefits observed in the current study might accurately reflect MK-0777 efficacy for neuropsychological test measures. Finally, the group difference in the combined POP/N-back reaction time measure was largely driven by marked slowing of POP RTs in the placebo group. The MK-0777 group showed modest RT decreases on the two measures. In the current study, the placebo participants exhibited decreased RT in two of the three 2-back measures, whereas there tended to be a minimal to small RT increase on these measures in the MK-0777 3 mg b.i.d. group and a minimal to small RT decrease on these measures in the MK-0777 8 mg b.i.d. group.

The MCCB composite score and each of the domain scores exhibited good to excellent test–retest reliability. The placebo group exhibited small but significant practice/learning effects for the MCCB composite score and the verbal learning and reasoning/problem-solving domains.

There are several potential limitations of the current study. The most important is that the sample size is relatively small, so there is a possibility of a type II error (i.e., MK-0777 is truly better than placebo), but there was not sufficient power to detect the difference. However, across all efficacy measures the observed changes were numerically better in the placebo group, and the only significant differences favored the placebo group. Moreover, the current study used a rigorous study design intended to minimize potential confounding variables in the evaluation of potential cognitive-enhancing drugs (30,34).

If the current study results accurately reflect the cognitive benefits of MK-0777, then what are the implications for future studies of GABA_A2 agonists? First, the rationale for the GABA_A2 target is compelling, with significant preclinical and clinical evidence to support the hypothesis that a drug that activates this receptor could have cognitive-enhancing effects. However, MK-0777 is a relatively weak GABA_A2 partial agonist, with 10%–20% of the potency of a full GABA_A2 agonist, and might not represent the most rigorous assessment of the hypothesized mechanism. Moreover, although MK-0777 is relatively selective for the GABA_A2 and GABA_A3 receptor units, new or worsened sedation was observed numerically more frequently in the experimental treatment arms than in the placebo arm. In the Lewis et al. study, somnolence was reported more frequently in the MK-0777 than placebo group. These sedative effects could have adversely affected cognitive performance—a hypothesis that receives partial support from the observation that participants randomized to MK-0777 were less likely than those randomized to placebo to exhibit practice/learning effects for the MCCB composite score. In combination, these considerations suggest that a more selective agent with greater intrinsic activity at the GABA_A2 site might still be worth pursuing for the treatment of cognitive impairments in schizophrenia.

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Sumitomo Pharma, GlaxoSmithKline, Lundbeck, Otsuka, Sanofi Aven-
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Glytech and Amino Acids Solutions. Over the past 2 years, Dr. Javitt has
served as a consultant for pharmaceutical companies, including
Sanofi Aventis, Solvay, Organon, Lundbeck, AstraZeneca, NPS Phar-
maceuticals, Takeda, and Sepracor. He currently serves on a new treat-
ment development advisory board for Pfizer, serves on the Scientific
Advisor Board for Promentis Pharmaceuticals, and has received re-
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Lundbeck, Memory Pharmaceuticals, Merck, Neurosearch, NeuroCog
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Pfizer, Sepracor, and Targacept and also served on advisory boards for
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Pharmaceuticals in the past 5 years. All other authors report no bio-
medical financial interests or potential conflicts of interest.

Clinicaltrials.gov: MK-0777 for the Treatment of Cognitive Im-
pairments in Patients With Schizophrenia; http://clinicaltrials.gov/
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