Attention Benefits After a Single Dose of Metadoxine Extended Release in Adults With Predominantly Inattentive ADHD

Iris Manor, MD1
Jonathan Rubin, MD, MBA2
Yaron Daniely, PhD, MBA3
Lenard A. Adler, MD4

1Associate Professor of Psychiatry, Geha Mental Health Center, Petah Tikva, Israel; 2Chief Medical Officer, Alcobra Inc, Plymouth Meeting, PA; 3Chief Executive Officer, Alcobra Ltd, Tel Aviv, Israel; 4Professor of Psychiatry and Child and Adolescent Psychiatry, New York University School of Medicine, New York, NY

Abstract

Objective: To assess the first-dose effectiveness and tolerability of metadoxine extended release (MDX) in adults with predominantly inattentive attention-deficit/hyperactivity disorder (ADHD-PI).

Methods: In this double-blind, placebo-controlled, crossover study, adults with ADHD-PI were randomized 1:1:1 to receive a single dose of MDX 1400 mg, MDX 700 mg, and placebo (ClinicalTrials.gov identifier: NCT01685281). The primary efficacy end point was the mean change in the Test of Variables of Attention (TOVA) ADHD score from baseline to 3 to 5 hours after drug administration. Secondary assessments included TOVA subscores, TOVA response rates (defined as an increase of 0.8 points in the TOVA ADHD score), and the Cambridge Neuropsychological Automated Test Battery. Safety assessments included adverse events and vital signs.

Results: The intention-to-treat population included 36 patients (52.8% men; mean age, 32 years). The efficacy of MDX 1400 mg was demonstrated by a statistically significant difference in the mean (± SD) change in the TOVA ADHD score at baseline to 3 to 5 hours after drug administration compared with placebo (2.0 [4.2]; P = 0.009). The TOVA response time variability subscore was significantly different between MDX 1400 mg and placebo (mean difference, 7.9 [19.2] points; P = 0.022). Significantly more adults responded to single-dose MDX 1400 mg versus placebo (97.1% vs 71.4%, P = 0.006). There were no statistically significant differences between MDX 700 mg and placebo on any measures. Exploratory analyses of the Cambridge Neuropsychological Automated Test Battery did not yield significant findings. Fatigue and headache were the 2 most frequently reported adverse events. There were no clinically significant abnormalities in laboratory values, vital signs measurements, Columbia–Suicide Severity Rating Scale scores, or electrocardiographic parameters.

Conclusions: Single-dose MDX 1400 mg significantly improved sustained and selective attention in adults with ADHD-PI as measured by the TOVA ADHD score 3 to 5 hours after drug administration. Single doses of MDX 700 and 1400 mg were well tolerated.

Keywords: cognition; executive function; continuous performance test; nonstimulant; MDX

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder associated with significant impairment throughout the lifespan of an affected individual.1,2 Once believed to be a childhood disorder, research currently indicates that > 50% of children diagnosed with ADHD will continue to display symptoms of the disorder through adolescence and into adulthood.3 Current estimates indicate that ADHD affects approximately 4% of adults in the United States.4 Based on the
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Presenting symptoms, a diagnosis of ADHD can be divided into 3 presentations: combined ADHD, which is a mix of inattentive and hyperactive-impulsive symptoms; predominantly hyperactive-impulsive ADHD, which is diagnosed in patients with mostly hyperactive-impulsive symptoms; and predominantly inattentive ADHD (ADHD-PI), diagnosed in those with primarily inattentive symptoms. As children with the disorder mature into adults, the ADHD-associated symptoms of hyperactivity and impulsivity tend to decrease as the symptoms of inattention increase: 95% of adults with ADHD report that they experience inattentive symptoms. In addition, ADHD is associated with increased health risks into adulthood, including higher rates of substance abuse, increased driving violations and accidents, employment difficulties, and marital problems. Therefore, effective treatment for adults with ADHD is necessary.

Previous studies of stimulant and nonstimulant medications for the treatment of ADHD in adults have generally reported similar efficacy in the management of inattentive and hyperactive-impulsive symptoms. Although symptoms of ADHD may be effectively treated with medication and/or psychosocial interventions in some adult patients, an unmet need exists for additional, well-tolerated treatment options. Psychostimulants have been extensively studied in clinical studies in children, and are effective and safe for the treatment of patients with ADHD; however, a substantial percentage of adults with ADHD who are prescribed stimulants for symptom management may not respond to or tolerate the medication. In addition, long-term use of stimulants is associated with increased heart rate and blood pressure, adherence is problematic, and there is the potential for abuse, misuse, and diversion of these controlled substances. Although there are a few nonstimulant treatments available for use in children and adolescents, atomoxetine (Strattera, Eli Lilly and Company, Indianapolis, IN), a selective norepinephrine reuptake inhibitor, is the only nonstimulant approved by the US Food and Drug Administration (FDA) for the treatment of children and adults with ADHD. Adverse events (AEs) associated with atomoxetine include potential effects on blood pressure and heart rate, sexual dysfunction, and suicidal ideation in children and young adults. Of note, treatment may be needed before the maximal therapeutic effect can be experienced.

Metadoxine extended release (MDX) is a nonstimulant medication in clinical development for the treatment of patients with ADHD. While MDX has been studied in this patient population during the last several years, metadoxine immediate release has been used for > 30 years as treatment for acute alcohol intoxication and alcohol withdrawal syndrome. Metadoxine is an ion-pair salt of pyridoxine (vitamin B6) and 2-pyrrolidone-5-carboxylate (PCA, also known as PGA [pyroglutamic acid]). Although the exact mechanism of action of MDX is unknown, preclinical studies suggest that metadoxine has a novel monoamine-independent mechanism of action and may have the potential to improve cognition in patients with ADHD.

Use of MDX in adults with ADHD was previously examined in a single-site, open-label study of 40 adults diagnosed with ADHD. In this study, a single dose of MDX 1400 mg was well tolerated and improved cognitive performance as measured by a mean increase of 3.9 points in the Test of Variables of Attention (TOVA) ADHD score from baseline ($P < 0.001$). In a 6-week randomized, double-blind, placebo-controlled study of 120 adults with ADHD, MDX 1400 mg was well tolerated and showed significant improvements in ADHD-associated symptoms compared with placebo as early as 2 weeks after treatment initiation. In a prespecified secondary analysis of MDX effect by ADHD subtype, Manor et al determined that MDX was preferentially effective for the treatment of inattentive symptoms in adults with ADHD-PI. Because MDX was determined to be effective and well tolerated in previous studies for the treatment of adults with ADHD, with a preferential response in those with ADHD-PI and a rapid onset of effect, the current randomized, double-blind, placebo-controlled, single-dose crossover study was conducted to evaluate the cognitive effects (as measured by the TOVA) and tolerability of single doses of MDX, 1400 and 700 mg, in adults with ADHD-PI.

Methods

The current study was a single-center, randomized, double-blind, placebo-controlled, crossover, single-dose, dose-finding study conducted between August 16, 2013, and November 26, 2013, at the ADHD Unit of the Gehr Mental Health Center in Petah Tikva, Israel (NCT01685281). The 5-week study consisted of a screening period (visit 1; day 1 to −7), baseline period (visit 2; day 0), 3-week crossover treatment period (visits 3, 4, and 5; days 7, 14, and 21 [± 3 days]), and 1-week follow-up period after the last visit for treatment (Figure 1). Patients were randomly assigned in a 1:1:1 ratio to 1 of 3 treatment sequences in which each patient received 1 dose of MDX 1400 mg, MDX 700 mg, and placebo (Figure 1).

Treatments were administered per treatment sequence during the 3-week crossover period, with the first treatment
Rapid Attention Benefits of MDX in ADHD

Figure 1. Treatment sequences.

<table>
<thead>
<tr>
<th>Treatment Week</th>
<th>Sequence 1 (n = 12)</th>
<th>Sequence 2 (n = 12)</th>
<th>Sequence 3 (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MDX 1400 mg</td>
<td>MDX 700 mg</td>
<td>Placebo</td>
</tr>
<tr>
<td>2</td>
<td>MDX 700 mg</td>
<td>Placebo</td>
<td>MDX 1400 mg</td>
</tr>
<tr>
<td>3</td>
<td>Placebo</td>
<td>MDX 1400 mg</td>
<td>MDX 700 mg</td>
</tr>
</tbody>
</table>

Screening Period | Treatment Period (Double-blind, Placebo-controlled) | Follow-up Period

V1 | Day 7 to −1 | washout |
V2 | Day 9       | washout |
V3 | Day 7       | Single Dosing |
V4 | Day 14      | Single Dosing |
V5 | Day 21      | Single Dosing |
V6 | Day 28      | Follow-up |

Abbreviations: MDX, metadoxine extended release; V, visit.

administered 1 week after randomization, the second administered 2 weeks after randomization, and the last administered 3 weeks after randomization. No treatment was allowed between study visits.

Before study initiation, written approval of the protocol was obtained from the study center’s ethics committee and other relevant regulatory authorities, including the Israeli Ministry of Health. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and its amendments, International Conference for Harmonisation-Good Clinical Practice guidelines, and local guidelines and regulations. Written informed consent was obtained from each patient before study participation.

Patients

The study included adult men and women aged 18 to 55 years diagnosed with ADHD-PI based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria as assessed by the Adult ADHD Clinical Diagnostic Scale, version 1.2. The Adult ADHD Clinical Diagnostic Scale has been validated as a structured, clinician-rated ADHD diagnostic scale that assesses the 18 adult and childhood symptoms of ADHD with age-specific prompts and allows the clinician to make a determination whether DSM-IV-TR adult ADHD is present. Each patient was evaluated at screening using various rating scales including the Structured Clinical Interview for DSM-IV (for other psychiatric comorbidities), Columbia–Suicide Severity Rating Scale (C-SSRS), State-Trait Anxiety Inventory, Beck Depression Inventory-II, TOVA version 7.3, four Cambridge Neuropsychological Automated Test Battery (CANTAB) cognitive tests, and the 7-point Clinical Global Impression–Severity scale (CGI-S). A moderate or greater level of ADHD clinical severity was defined as a CGI-S score of ≥ 4 and a TOVA ADHD score of ≤ −1.8 at baseline. The Behavior Rating Inventory of Executive Function—Adult version (BRIEF-A) was assessed at the randomization visit, and included 3 composite scores: Global Executive Composite, Behavioral Regulation Index, and Metacognition Index.

Patients presenting with ADHD not otherwise specified or any significant medical condition (HIV-positive, AIDS, hepatitis C, hepatitis B, or tuberculosis) or psychiatric condition (bipolar disorder, psychosis, schizophrenia, depression, suicidality, or any current Axis I diagnosis) were excluded from the study. Adults who previously did not respond to adequate trials of ≥ 2 ADHD treatments were excluded, as well as patients taking any psychiatric medications, including ADHD stimulant medications, 14 days before screening or nonstimulant and other psychotropic medications 28 days before screening. Patients with known allergies or sensitivities to B-complex vitamins or those who were currently using any vitamin B formulation were also excluded; patients receiving any investigational treatment in the previous month were also excluded. Also excluded were patients with current or recent history of drug dependence or substance abuse disorder. Patients included in the study had to agree not to change caffeine consumption considerably during the study.

Efficacy

The TOVA is a neuropsychological continuous performance test that was assessed 3 to 5 hours after drug administration at each treatment visit (days 7, 14, and 21), and then was compared with baseline values. The TOVA uses computerized responses to geometric stimuli (to minimize the effect of cultural differences and learning patterns) to provide information about a patient’s sustained attention, speed and consistency of responding, and behavioral self-regulation and executive functioning. Version 7.3 of the TOVA was used to assess patients, which generated an overall score (TOVA ADHD score) and 5 subscores: response time variability (measures inconsistency in response time), response time (measures actual time to respond), commission errors (measures impulsivity), omission errors (measures inattention), and D-prime (measures performance deterioration over time). The TOVA is a valid and reliable method to measure attention and impulsivity and can be used to monitor treatment response.
The CANTAB is a battery of computerized tests that assess key cognitive deficits present in ADHD. Computerized testing allows complex stimuli to be generated and presented to patients with responses recorded automatically and with precision. Four CANTAB cognitive tests were used in the study: spatial working memory, stop signal task, rapid visual information processing, and reaction time. The four CANTAB cognitive assessments were measured 3 to 5 hours after drug administration at each treatment visit (days 7, 14, and 21), and the results were compared with baseline values from the randomization visit.

Data from the screening visit were considered baseline values for statistical analysis for the TOVA, and, for the CANTAB tests, data from the randomization visit were considered baseline values. Mean change from baseline to 3 to 5 hours after drug administration for the TOVA ADHD score was the primary efficacy end point. Mean change in TOVA subscores and TOVA response rate, defined as an improvement of ≥ 0.8 points in the TOVA ADHD score, were considered secondary efficacy end points. In the current study, the four CANTAB tests were used as exploratory measures to evaluate cognitive performance 3 to 5 hours after drug administration. Mean changes from baseline to after drug administration in the four CANTAB scores were considered secondary/exploratory efficacy end points.

Safety
At each treatment visit, patients were evaluated for vital signs, concomitant medications were documented, and AEs were recorded. Safety assessments were based on changes from baseline in clinical AEs; reports of concomitant medication use and treatment compliance; findings from vital sign measurements; findings on electrocardiographic (ECG) tracings; results from the C-SSRS; and results from physical examination, neurological examination, and laboratory assessments (hematology, blood chemistry, and urinalysis).

Adverse Events
All AEs from screening to follow-up visits were reported during the study, and were considered to be any adverse change from the patient’s baseline condition, whether or not the AE was determined to be related to MDX therapy. All AEs were reported and rated by the investigator for severity, seriousness, and relationship to study drug, and coded according to the Medical Dictionary for Regulatory Activities, version 16.1.

Laboratory Values
All clinical laboratory assessments were performed by American Medical Laboratories (Herzliya Pituach, Israel). Routine laboratory sampling was performed at screening and follow-up visits.

Vital Signs and ECGs
Vital sign measurements were obtained at screening, on each dosing day (days 7, 14, and 21), and at follow-up, and included body temperature, respiration, blood pressure, and resting heart rate. A 12-lead ECG was performed at screening and follow-up visits. Results of the ECG were evaluated by the investigator, and in cases of potentially clinically significant findings, a cardiologist was consulted. Abnormal vital sign values were considered a heart rate < 50 or > 100 beats per minute (bpm), systolic blood pressure < 90 or > 140 mm Hg, and diastolic blood pressure > 90 mm Hg.

Statistical Analysis
The intention-to-treat (ITT) population and safety populations included all randomized patients who received ≥ 1 dose of study treatment. All tests applied were 2-tailed, and a P value of ≤ 0.05 was considered to be statistically significant. Analysis of variance was applied to test the carry-over effect in the primary efficacy end point between the 3 treatment sequences. Paired t tests for 2 means (paired observations) were applied to examine the statistical significance of the mean changes from baseline and mean differences between treatment with MDX 1400 mg versus placebo and MDX 700 mg versus placebo. $X^2$ tests were applied to analyze the differences in response rates between treatments, but for analyses with < 5 observations, Fisher’s exact test was used. Data were analyzed using SAS, Version 9.1 (SAS Institute, Cary, NC). For the primary and secondary end points, a subgroup analysis by sex was completed.

With an 80% probability to detect a treatment difference at $\alpha = 0.05$ (2-sided), a sample size of 36 adults (12 patients per treatment sequence) was required to show a difference between active treatment and placebo of 2.5 units in the primary efficacy end point (mean change in TOVA ADHD score from baseline to 4 hours after drug administration).

Results Patients
Of the total number of randomized patients (N = 36), 35 were diagnosed with ADHD-PI based on DSM-IV-TR criteria for ADHD, and 1 patient had symptoms consistent with ADHD-PI based on DSM-5 criteria with an onset of...
ADHD symptoms at age 7 years. At screening, CGI-I scores indicated that half of patients were “markedly ill,” 22.2% were “moderately ill,” and 27.8% were “severely ill.”

Of the total study population, 52.8% (n = 19) were men. The mean (± SD) age was 31.9 (6.7) years (range, 18.0–45.8 years), and the mean weight was 70.8 (15.7) kg (range, 46.0–104.2 kg). Most patients (77.8%; 28 of 36) had > 12 years of education. At baseline, the mean Behavior Rating Inventory of Executive Function-Adult version Global Composite Executive score was 139.4 (20.5), the mean Behavioral Regulation Index was 53.7 (9.4), and the mean Metacognition Index was 85.7 (15.0). The mean systolic blood pressure was 116.3 (10.3) mm Hg, mean diastolic blood pressure was 72.6 (7.2) mm Hg, and mean pulse was 65.2 (8.8) bpm.

The study randomized the 36 patients to each of the 3 possible treatment sequences (12 to each sequence; Figure 1) and 34 (94.4%) completed the study. The 2 patients that were withdrawn from the study were randomized to the MDX 700 mg, placebo, MDX 1400 mg sequence. Of the 2 patients that failed to complete the study, 1 was withdrawn at the request of the sponsor because of protocol violation (the patient took an antihistamine, a prohibited concomitant medication that could interfere with their performance on the TOVA); this patient received the MDX 700-mg dose and was withdrawn before receiving the placebo dose and the MDX 1400-mg dose. The other patient was withdrawn because of noncompliance (this patient received the MDX 700-mg and placebo dose, but did not appear for the final 2 visits: MDX 1400-mg dose visit and final follow-up visit). Both patients were included in the ITT analysis group.

### Table 1. TOVA ADHD Scores by Treatment (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>MDX 1400 mg (n = 34)</th>
<th>MDX 700 mg (n = 36)</th>
<th>Placebo (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOVA ADHD score post-dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>−2.5 (5.3)</td>
<td>−4.1 (5.6)</td>
<td>−4.4 (6.4)</td>
</tr>
<tr>
<td>Change from baseline in TOVA ADHD score</td>
<td>6.3 (4.5)</td>
<td>4.7 (5.4)</td>
<td>4.4 (6.6)</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.1, 4.9</td>
<td>6.5, 2.9</td>
<td>6.7, 2.2</td>
</tr>
<tr>
<td>F value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>TOVA ADHD subscores post-dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response time variability</td>
<td>83.7 (27.0)</td>
<td>74.1 (28.1)</td>
<td>76.0 (25.8)</td>
</tr>
<tr>
<td>Response time</td>
<td>100.9 (19.8)</td>
<td>94.8 (21.7)</td>
<td>96.7 (19.7)</td>
</tr>
<tr>
<td>Commission errors</td>
<td>99.0 (18.7)</td>
<td>96.8 (25.0)</td>
<td>95.2 (20.5)</td>
</tr>
<tr>
<td>Omission errors</td>
<td>83.4 (26.2)</td>
<td>73.8 (27.4)</td>
<td>77.4 (31.2)</td>
</tr>
<tr>
<td>D-prime</td>
<td>85.4 (28.2)</td>
<td>76.6 (26.4)</td>
<td>79.9 (28.0)</td>
</tr>
</tbody>
</table>

*As measured 3–5 hours after drug administration.

*Versus baseline (paired t test).

*Statistically significant change versus placebo (P = 0.022) and versus MDX 700 mg (P = 0.018).

**Abbreviations:** ADHD, attention-deficit/hyperactivity disorder; ITT, intention-to-treat; MDX, metadoxine extended release; TOVA, Test of Variables of Attention.
TOVA ADHD Subscores
Of the TOVA subscores, the mean change from baseline to after drug administration in the response time variability score (measurement of the quantity of inattention/sustained attention) was significantly different between MDX 1400 mg and placebo (mean [SD] difference, 7.9 [19.2] points; \( P = 0.022 \); Table 1). There were no statistically significant differences seen between MDX 700 mg and placebo in the TOVA ADHD subscores. The mean response time, commission errors, omission errors, and D-prime scores were significantly increased from baseline to 3 to 5 hours after drug administration for all study treatments, but the differences in changes between MDX and placebo for these four TOVA ADHD subscores did not reach statistical significance. The mean difference in change scores between MDX 1400 mg and placebo approached statistical significance for both commission errors (mean [SD] difference, 4.3 [13.0] points; \( P = 0.061 \)) and D-prime scores (mean [SD] difference, 6.5 [22.8] points; \( P = 0.108 \)).

The percentage of responders (those experiencing an improvement of \( \geq 0.8 \) points in TOVA ADHD score) 3 to 5 hours after a single dose of MDX 1400 mg (n = 33; 97.1%) was significantly greater compared with placebo (n = 25; 71.4%; \( P = 0.006 \); Figure 3). No difference in the percentage of responders was shown between MDX 700 mg and placebo.

CANTAB Scores
Exploratory analyses of the four CANTAB test scores did not yield significant findings. Changes in CANTAB scores from baseline to 3 to 5 hours after drug administration did not differ significantly between treatments after only 1 dose of study medication.

Subgroup Analysis
The mean TOVA ADHD score at baseline was −10.2 (SD, 7.0) in men and −7.4 (SD, 5.2) in women. There was a significant change in the TOVA ADHD score from baseline to 3 to 5 hours after single-dose MDX 1400 mg in men and women (mean [SD] improvement, 6.7 [5.2] and 6.3 [3.8] points, respectively); however, the difference between the change in TOVA ADHD score between MDX 1400 mg and placebo was statistically significant only among men (mean [SD] difference, 2.2 [3.9] points; \( P = 0.027 \)). Differences between the mean changes in the TOVA ADHD scores after a single dose of MDX 700 mg versus placebo were not statistically significant in men or women (data not shown).

Safety
Both doses of MDX (700 and 1400 mg) were well tolerated, as demonstrated by AEs, laboratory results, vital sign measurements, ECG parameters, C-SSRS results, and findings on physical and neurological evaluations.

Adverse Events
Of the 36 patients enrolled, 63.9% (n = 23) experienced 51 AEs during the study, and 55.6% (n = 20) experienced 37 treatment-emergent AEs (TEAEs). A total of 37 TEAEs occurred during active treatment and follow-up periods, of which 28 (75.7%) were suspected of being related to study treatment. The inci-
The incidence of TEAEs was similar with MDX 1400 mg and placebo, with the lowest incidence of TEAEs occurring after single-dose MDX 700 mg. Fatigue and headache were the 2 most frequently reported TEAEs (and occurred with a similar incidence) after single-dose MDX 1400 mg or placebo (Table 2).

Nearly all AEs (94.1%) were mild in severity except for 3 moderate AEs of headache in 2 (5.9%) patients (Table 2): 1 patient reported a headache after a single placebo dose and after a single MDX 700-mg dose, and the other patient reported headache after single-dose MDX 700 mg. There were no severe or serious AEs. Most AEs lasted ≤ 1 day and resolved without sequelae.

Overall, 34 (94.4%) of the 36 patients completed the study. The 1 AE that led to study discontinuation was an allergic reaction (dermatitis) that required treatment with an antihistamine (discussed previously), a prohibited concomitant medication, and the patient was withdrawn from the study at the request of the sponsor (Alcobra Ltd). A second patient was discontinued from the study because of noncompliance; the patient did not attend the final treatment or follow-up visit (discussed previously).

Vital Signs and ECGs

There were no clinically significant abnormalities in vital sign measurements or ECG parameters or findings at clinical examination. Mean values of vital signs were within normal limits for all measurements at screening and follow-up.

Similar results were observed during treatment administration. Mean (SD) changes in systolic and diastolic blood pressures before and after drug administration were 3.97 (10.44) and −0.73 (7.38) mm Hg, respectively, for the MDX 1400-mg dose; 1.33 (10.93) and 0.44 (6.91) mm Hg, respectively, for the MDX 700-mg dose; and −0.62 (9.18) and −1.62 (9.01) mm Hg, respectively, for placebo. Mean blood pressure changes were not considered clinically significant. The mean (SD) change in pulse before and after drug administration was −2.12 (8.55) bpm for the MDX 1400-mg dose, −0.11 (8.69) bpm for the MDX 700-mg dose, and −2.0 (11.92) bpm for placebo; mean changes in pulse were not considered clinically significant. No individual vital sign abnormalities were considered to have been clinically significant or considered AEs.

Electrocardiographic results were normal in 33 of 36 patients at baseline and at follow-up, with no new or clinically significant abnormalities reported after MDX or placebo treatment.

**Table 2.** Number and Percentage of Patients With AEs, Total Number of AEs, AE Severity, and Discontinuations Due to AEs

<table>
<thead>
<tr>
<th></th>
<th>MDX 1400 mg (n = 34)</th>
<th>MDX 700 mg (n = 36)</th>
<th>Placebo (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ⩾ 1 AE, n (%)</td>
<td>11 (32.4)</td>
<td>6 (16.7)</td>
<td>11 (31.4)</td>
</tr>
<tr>
<td>Total AEs, N (35)</td>
<td>14</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Total mild AEs, n (%)</td>
<td>14 (100)</td>
<td>7 (77.8)</td>
<td>11 (91.7)</td>
</tr>
<tr>
<td>Total moderate AEs, n (%)</td>
<td>0</td>
<td>2 (22.2)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Patients with AEs possibly related to study drug, n (%)</td>
<td>8 (23.5)</td>
<td>5 (13.9)</td>
<td>7 (20.0)</td>
</tr>
<tr>
<td>Fatigue, n (%)</td>
<td>5 (14.7)</td>
<td>0</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Headache, n (%)</td>
<td>3 (8.8)</td>
<td>2 (5.6)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Patients who discontinued due to AE, n (%)</td>
<td>0</td>
<td>1 (2.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Abbreviations:** AE, adverse event; MDX, metadoxine extended release.
A significant clinical improvement in TOVA ADHD scores was observed at week 6 in those receiving MDX 1400 mg compared with placebo (mean increase, 5.0 vs 3.0 points; \( P = 0.02 \)), with separation from placebo evident as early as week 1. A secondary analysis of patients with ADHD-PI (\( n = 48 \)) by Manor et al revealed a statistically significant change in TOVA ADHD score from baseline to end point that was of larger magnitude than seen in the entire sample compared with placebo (6.7 vs 2.8; \( P < 0.05 \)).

Notably, patient improvement with administration of MDX was observed in the TOVA ADHD subscore measures that provide vital information about a patient’s response style including tendency to make impulsive errors (commission errors), tendency to make errors because of inattention or distraction (omission errors), distractibility (D-prime), and pace of reaction time (response time). However, the only statistically significant difference in TOVA subscores between MDX 1400 mg and placebo (\( P = 0.022 \)) was in the consistency of reaction time (ie, the response time variability subscore), which measures the quantity of inattention/sustained attention. Of note, the TOVA response time variability subscore may be a biomarker for inattention in all patients with ADHD (not only in patients with ADHD-PI). Therefore, this statistically significant improvement in the quantity of inattention/sustained attention 3 to 5 hours after a single dose of MDX 1400 mg highlights the promise of MDX as a potentially effective agent with preferential activity in patients with ADHD-PI.

Although most (97.1\%) of the patients responded to treatment after a single 1400-mg MDX dose (response defined as improvement of \( \geq 0.8 \) points in TOVA ADHD score), changes in cognitive deficits as assessed by the CANTAB computerized tests were not significantly different between treatments. Medication trials in patients with ADHD have shown inconsistent results with CANTAB tests, and in this study, exploratory analyses of the four CANTAB tests did not yield statistically significant findings. One possible reason for the lack of statistically significant findings in CANTAB results despite the high percentage of reported responders (as measured by the TOVA) might be that the current study was not powered fully to detect change in the CANTAB tasks as it was for the TOVA. In addition, the CANTAB tests were measured after only 1 dose of study medication and different results may be seen with a longer duration of treatment and a larger patient sample.

Subgroup analysis by sex showed that the difference in mean TOVA ADHD score was statistically significant for men (\( P = 0.027 \)), but not for women. Interestingly, these results are similar to those reported by Braverman et al, who performed a statistical analysis of outcomes in adults screened for ADHD and showed that the TOVA was an accurate predictor of attention symptoms in the clinical setting, but that the findings were more obvious and robust for the population of men than for women. Additionally, Huang et al also reported that sex appears to have an influence in the assessment of treatment effects as measured by the TOVA. However, the most likely reason that the difference in mean TOVA ADHD score for MDX 1400 mg compared with placebo was not statistically significant for women in the current study is because women had a higher mean baseline TOVA ADHD score than men (\( -7.4 \pm 5.2 \) vs \( -10.2 \pm 7.0 \)); therefore, the mean change after drug administration did not reach statistical significance because of a floor effect (ie, women were less impaired at baseline).

The magnitude of MDX effect as measured by the TOVA ADHD score in this study was consistent with the effect measured in 2 previous studies in adults with ADHD-PI. In the current study of patients with ADHD-PI, the effect size of MDX 1400 mg versus placebo as measured by the mean change in TOVA ADHD score was 0.48, and the mean change in the TOVA ADHD score from baseline after a single MDX 1400-mg dose was 6.5. In the initial open-label proof-of-concept study in 40 adults with ADHD, the mean change in the TOVA ADHD score from baseline after a single MDX 1400-mg dose was 4.2 in the subset of 20 patients with ADHD-PI. In a 6-week study of 120 adults with ADHD, the MDX effect size (based on the mean change in the TOVA ADHD score) was 0.50 in a subset of 48 adults with ADHD-PI (data on file, Alcobra Ltd), and the mean TOVA ADHD score increased by 5.0 points from baseline to end point. Other clinical trials of ADHD medications in adults have not used the TOVA ADHD score as a primary efficacy end point, making comparison of effect sizes across studies of other agents difficult.

The rapid onset of effect (within 3 to 5 hours) as measured by the TOVA distinguishes MDX from atomoxetine, the only nonstimulant medication approved in the United States for the treatment of adults with ADHD. Use of the TOVA to assess atomoxetine response is not recommended by the TOVA developers, and, to the authors’ knowledge, no comparable studies using the TOVA to assess the single-dose response to atomoxetine in adults with ADHD have been published. Medication studies using clinical rating scale assessments indicate that atomoxetine may require several weeks before a significant therapeutic effect is evident and requires dose
Similar to most ADHD medication studies, this study also excluded known nonresponders to ADHD treatment and patients with major depressive disorder, significant anxiety, suicidality, or drug or alcohol dependence, potentially limiting the generalization of findings to the entire ADHD population.

Consistent with the previous 6-week study of MDX 1400 mg in 120 adults with ADHD, there were no clinically significant abnormalities or related AEs reported for any vital sign. There were no consistent differences in vital signs between MDX and placebo treatment groups and no cumulative changes over time.

Conclusions
This single-dose crossover study demonstrated a statistically significant effect of MDX 1400 mg compared with MDX 700 mg and placebo as assessed by the TOVA ADHD score 3 to 5 hours post-dose. Furthermore, the magnitude of the effect on the TOVA ADHD scores was similar to the effect observed in previous trials of MDX in adults with ADHD. Single doses of MDX were well tolerated. Larger, multiple-dose studies are needed to further assess the safety and efficacy of MDX 1400 mg in adults with ADHD.

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Conflict of Interest Statement
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References


