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Efficacy of Metadoxine Extended Release in Patients With Predominantly Inattentive Subtype Attention-Deficit/Hyperactivity Disorder

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Abstract

Objectives: To compare the effects of metadoxine extended release (ER) with those of placebo on inattentive (IA) versus hyperactive-impulsive (H-I) symptoms and predominantly inattentive (PI) versus combined type (CT) subtype in adults with attention-deficit/hyperactivity disorder (ADHD). **Methods:** This was a 1:1 randomized, double-blind, parallel-design study of metadoxine ER 1400 mg/day for 6 weeks in 120 adults with ADHD. Efficacy measures were baseline to end-of-treatment changes in Conners' Adult ADHD Rating Scale–Investigator Rated (CAARS-INV) Total ADHD Symptoms scores with adult ADHD prompts, the Test of Variables of Attention ADHD scores, and response rates ($\geq 25\%$ or $\geq 40\%$ improvement in CAARS-INV Total ADHD Symptoms score). **Results:** There was a significant decrease in CAARS-INV Total ADHD Symptoms scores in patients with ADHD-PI taking metadoxine ER (40%) compared with those taking placebo (21%) ($P < 0.05$), while the decrease for patients with ADHD-CT was not significant (27% vs 26%). Similarly, there was a significant decrease in IA scores in patients with ADHD-PI (metadoxine ER, 50% vs placebo, 23%; $P < 0.005$), while the change in patients with ADHD-CT was not significant. There was no significant difference in percent decreases seen in H-I scores for patients with PI or ADHD-CT. Significantly higher response rates at both cutoffs (ie, 25% and 45% improvement) were seen in the metadoxine ER group compared with the placebo group in CAARS-INV Total ADHD Symptoms scores in patients with ADHD-PI, but not those with ADHD-CT. Test of Variables of Attention ADHD scores were significantly decreased in the metadoxine ER group compared with the placebo group for patients with ADHD-PI, but not those with ADHD-CT. **Conclusion:** These data suggest that metadoxine ER is selectively efficacious for treating IA symptoms in adults with ADHD-PI.

Keywords: attention-deficit/hyperactivity disorder; metadoxine; clinical trial; inattention

Trial registration: www.ClinicalTrials.gov identifier NCT01243242

Introduction

Once thought to be an affliction confined to childhood, attention-deficit/hyperactivity disorder (ADHD), a highly impairing neuropsychiatric condition, has been shown to persist into adolescence and adulthood. Research shows that more than half of all children with ADHD continue to have the disorder in adulthood.¹ Inattentive (IA) symptoms predominate the presentation of adult ADHD, with 95% of adults experiencing symptoms of inattention, and approximately one-third experiencing significant symptoms of hyperactivity-impulsivity (H-I).² Adult ADHD is highly prevalent, with 4.4%

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of adults believed to have some subtype of ADHD (predominately inattentive [PI], predominately H-I, or combined type [CT]).³

Adult ADHD is associated with increased health risks; health care costs; divorce rates; risks for motor vehicle accidents; higher rates of substance abuse, incarceration and other concurrent psychiatric conditions, such as substance use disorders, bipolar disease, and depression; and lower levels of socioeconomic attainment, academic achievement, and steady employment.⁴⁻⁷

Although symptoms of ADHD are significantly ameliorated with medication and/or psychosocial intervention, many issues remain that can impede positive clinical outcomes. Nine of 10 individuals who experience ADHD symptoms are undiagnosed and untreated.³ Yet even individuals treated with medication experience significant difficulties. While the psychostimulants methylphenidate and amphetamine have been shown to be effective and safe for the treatment of ADHD in adults, a sizeable percentage of those who are prescribed stimulants for ADHD either do not respond to or do not tolerate stimulant treatment.⁸ In addition, up to two-thirds of those prescribed ADHD medication do not adhere to treatment due to side effects.⁹ Concerns over potential abuse, misuse, or diversion may also limit the utility of stimulants in adults with ADHD.¹⁰⁻¹³ Finally, even among the best responders to stimulants, there are often time-action issues due to the short behavioral half-life of these medications.

Atomoxetine, a selective norepinephrine reuptake inhibitor, is the only nonstimulant approved by the US Food and Drug Administration for use in adults.¹⁴ While improvements can be substantial in some individuals, the overall effect size is only moderate. Other nonstimulants, such as guanfacine and clonidine, both α_{2A} adrenergic receptor agonists, are approved only for children and adolescents with ADHD.¹⁵

Metadoxine extended release (ER) is a nonstimulant pharmacotherapeutic agent that is currently being investigated for the treatment of ADHD. Metadoxine is a salt of pyridoxine (vitamin B6) and 2-pyrrolidone-5-carboxylate. Pyridoxine is an antecedent of coenzymes such as pyridoxal phosphate. Pyridoxal phosphate-dependent enzymes are vital in the biosynthesis of 4 basic neurotransmitters: epinephrine, norepinephrine, γ -aminobutyric acid, and serotonin.¹⁶ Metadoxine has been used over the past few decades to treat acute alcohol intoxication and alcohol withdrawal syndrome.¹⁷⁻¹⁹ Metadoxine ER is an ER oral formulation of metadoxine (hereafter referred to as metadoxine ER).

In 2012, Manor et al²⁰ reported a controlled trial of metadoxine ER, which found that the medication was well tolerated and efficacious in the treatment of adult ADHD. This study was a randomized, double-blind, controlled investigation of metadoxine ER 1400 mg/day compared with placebo (equal randomization) for 6 weeks, following a 2-week baseline/screening period and preceding a 2-week follow-up period involving 120 adults with ADHD. Compared with placebo treatment, metadoxine ER resulted in a statistically significant decrease in Conners' Adult ADHD Rating Scale- Investigator Rated (CAARS-INV) Total ADHD Symptoms scores ($P = 0.019$), a significant improvement in Test of Variables of Attention (TOVA) ADHD scores ($P = 0.02$), and a significant improvement in Adult ADHD Quality of Life (AAQoL) total scores ($P = 0.009$). Significant improvement in CAARS-INV Total ADHD Symptoms scores were documented after 2 weeks of metadoxine ER treatment compared with scores of patients treated with placebo.

Based on the TOVA finding of cognitive improvement in patients treated with metadoxine ER and our long-standing interest in examining the effects of the medication on inattention symptoms specifically, we thought it potentially useful to study the effects of metadoxine ER on inattention symptoms in adults with ADHD, and particularly those with the IA subtype. Although there are not yet published data on any ADHD treatment to indicate selective improvement in symptoms in the inattention domain as a function of subtype, there are data to suggest that patients with the IA subtype may respond differently to medication. For example, Stein et al²⁰ found that youth with IA subtype required lower stimulant doses than youth with CT subtype. This finding was subsequently replicated with a different formulation of methylphenidate and also amphetamine.²¹ While it is reasonable to assume that this difference might have been accounted for by lower severity in the IA subtype, it raises the question of differential medication response in the PI subtype.

We therefore conducted a series of analyses (pre hoc) to examine the effects of metadoxine ER compared with those of placebo on ratings of inattention symptoms and neuropsychological measurement of cognitive function (via the TOVA) in adults with ADHD in the study previously reported by Manor et al.²²

Methods

Subjects

As reported previously,²² subjects included in the study were adult men and women, aged 18 to 50 years, who were diagnosed with ADHD based on *Diagnostic and Statistical*

Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria as assessed by the Adult ADHD Clinical Diagnostic Scale version 1.2 (ACDS v1.2),²³ the Structured Clinical Interview for DSM-IV (SCID),²⁴ and a Clinical Global Impression Severity (CGI-S)²⁵ scale score ≥ 4 . Patients were classified by ADHD subtype per DSM-IV criteria as PI, CT, or H-I types.

Study Design

This study was a multisite, randomized, double-blind, placebo-controlled, phase 2 study of metadoxine ER administered at a target dose of 1400 mg/day for 6 weeks compared with placebo in a 1:1 ratio of 120 adults with ADHD. The study consisted of 3 periods: 1) a screening period of ≤ 2 weeks, 2) a 6-week double-blind treatment period, and 3) a 2-week safety follow-up period after cessation of treatment, described as follows:

Screening Period

Visit 1 (day -14 to 0): After obtaining informed consent, screening procedures were performed, including a battery of rating scales for confirmation of ADHD diagnosis (eg, the ACDS v1.2) and exclusion of other significant psychiatric comorbidities as assessed by the SCID. Additional assessments were performed using the TOVA,²⁶ the CGI-S,²⁵ the AAQoL,²⁷ and the CAARS-INV with adult ADHD prompts^{23,28,29} (scales are described in the following sections).

Safety assessments were as described previously.²² All raters were trained on all rater assessments (ACDS v1.2, CGI-S, and CAARS-INV, with adult prompts) per established training principles.³⁰

Treatment Period

Visit 2 (day 0), visit 3 (day 7), visit 4 (day 14), visit 5 (day 28), and visit 6 (day 42): At visit 2, eligible and consenting subjects were randomized in a 1:1 ratio to metadoxine ER 1400 mg or placebo. Subjects were instructed to take the medication once daily at the start of their day until the next scheduled visit. There was no titration period. At study visits 3, 4, 5, and 6, subjects underwent evaluations using the CAARS-INV, TOVA, and AAQoL to assess treatment response.

At each visit, subjects also underwent safety assessments. Study drug (used and unused) was collected at each of these visits for accountability purposes. Subjects who met 85% treatment adherence were included in the efficacy per-protocol analysis.

Follow-up Period

Visit 7 (day 56): 2 weeks after end of treatment, subjects underwent safety assessments. Following an amendment to the study, most subjects were also evaluated at this point using the CAARS-INV, TOVA, and AAQoL.

The primary efficacy measure was the change in CAARS-INV Total ADHD Symptom score between the study groups from baseline/screening to treatment termination. Secondary measures compared differences between the baseline/screening visit and end of treatment with respect to: 1) response rates as measured by percent of patients who achieved a predefined decrease (25% or 40%) in CAARS-INV Total ADHD Symptoms score; 2) change in the TOVA ADHD score; and 3) change in the AAQoL total score.²²

The CAARS-INV Total ADHD Symptom score (Subscale C) measures the 18 ADHD symptoms described in the DSM-IV, including the 9 symptoms of inattention (Subscale A) and the 9 symptoms of hyperactivity/impulsivity (Subscale B), each rated on a scale from 0 (none/never) to 3 (severe/very often) on a severity/frequency basis. Each item has a set of adult ADHD prompts to ensure adequate exploration of ADHD symptomatology. The TOVA is a computerized continuous performance test that measures variability of response time (consistency), response time, commission (impulsivity), errors of omission (inattention), post-commission response times, signal detection theory, which measures how quickly one's performance deteriorates over the 21.6 minutes of testing, and an ADHD score, which is a comparison to an age-/sex-specific ADHD group. The AAQoL measures quality of life in adults with ADHD in 5 areas: work, daily activities, relationships, psychological well-being, and physical well-being. The AAQoL includes 29 items that are rated on a frequency or severity basis on a scale from 1 (never/not at all) to 5 (very often/extremely) and are split into 4 domains: life productivity, psychological health, life outlook and relationships.

Statistical Analysis

Efficacy analysis was conducted on the intent-to-treat population. The efficacy analyses used 2-sample *t* test and nonparametric Mann-Whitney test, and the median test for independent samples for testing the statistical significance of the difference in changes in CAARS-INV Total ADHD Symptoms scores for patients taking metadoxine ER compared with those taking placebo from screening (visit 1) to end of treatment (visit 6). Analysis of covariance was used to compare group differences between the PI and CT subtypes in changes from visit 1 to 6 in both the primary endpoint and secondary

endpoint scales with adjustment for confounders (ie, baseline score, site, age, and sex). Testing differences between the groups in changes in efficacy parameters (CAARS-INV, TOVA, and AAQoL scores) from visit 6 to 7 was done using *t* tests. Paired *t* test was applied for testing within-group changes in efficacy parameters (CAARS-INV, TOVA, and AAQoL scores) from visit 6 to 7. Chi-square test and logistic analyses with adjustment to baseline score, sex, site, and age were applied for testing the statistical significance of the difference in the rate of responders between the study groups. All tests applied were 2 tailed, and a *P* value ≤ 0.5 was considered statistically significant.

For the responder analysis, treatment response rates were established as a 25% and 40% decrease in CAARS-INV total ADHD symptom scores from baseline to week 6, as defined previously in a trial on adult ADHD treatment with atomoxetine.³¹ The 2 subtypes were compared by percentage of patients who achieved entry-level or solid responder status using the definitions provided in the previous section.

Results

Demographics

Of the 174 screened subjects, 54 were excluded, primarily because of exclusionary psychiatric comorbidity. The remaining 120 subjects who satisfied all inclusion and exclusion criteria were randomized, 60 to metadoxine ER and 60 to placebo (Figure 1). The age, height, weight, and sex distributions, and educational background of the sample did not significantly differ between the metadoxine ER and placebo groups. All randomized subjects had a childhood onset of

ADHD (before age 7 years) and persistence of symptoms into adulthood. Of the 120 subjects, 69 (57.5%) had ADHD-CT, while 49 (40.8%) had ADHD-PI. Only 2 subjects, 1 in each arm, had H-I ADHD.

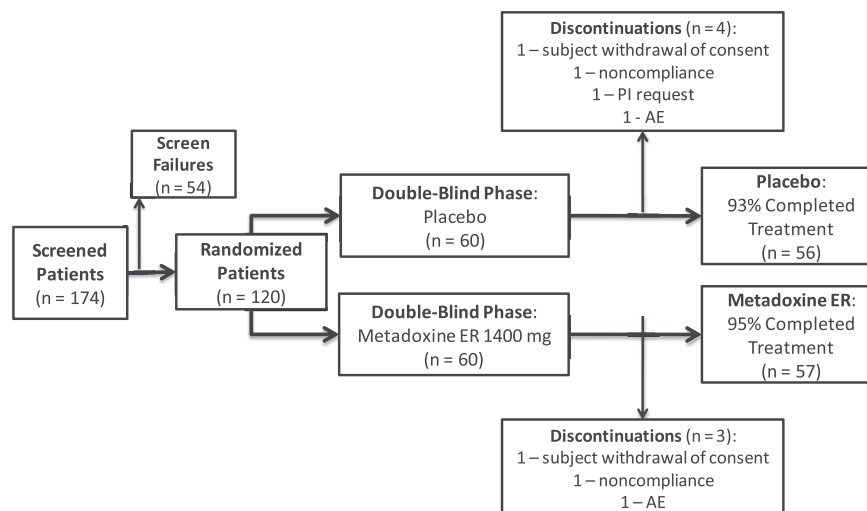
ADHD Symptom Evaluations

Figure 2 depicts 6 graphs showing the changes in CAARS-INV Total ADHD score (Subscale C), Subscale A score, and Subscale B score for patients taking metadoxine ER compared with those taking placebo. The first pair is Total ADHD score, the second pair is the Subscale A score (for IA symptoms only), and the last pair is the Subscale B score (for H-I symptoms only). The left column reflects CAARS-INV scores for patients with ADHD-PI and the right column reflects scores for patients with ADHD-CT.

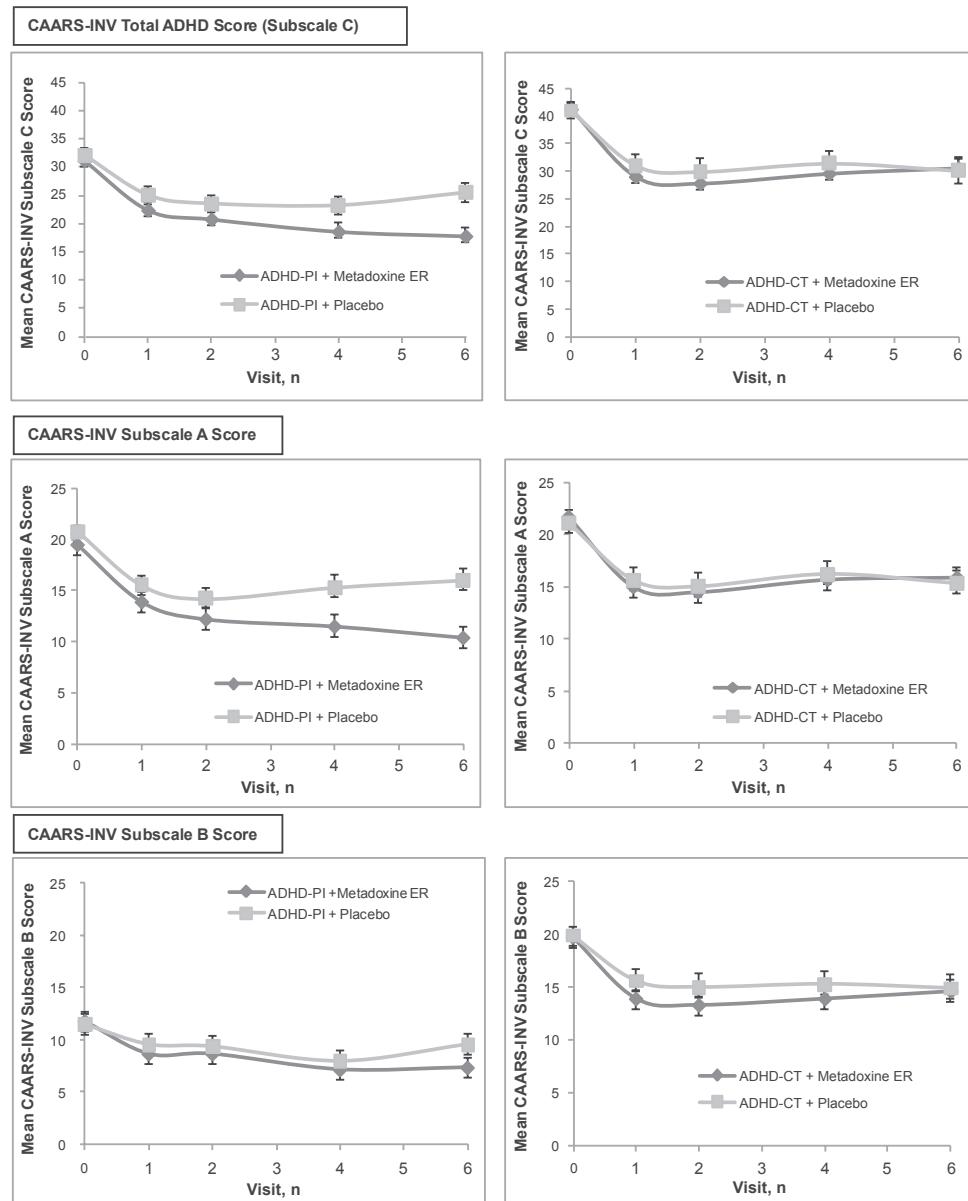
Mean (standard deviation [SD]) CAARS-INV Subscale C score for patients with ADHD-PI decreased from 31.1 (5.0) at baseline to 17.7 (7.5) at visit 6 in the metadoxine ER cohort, while a decrease from 32.1 (6.7) at baseline to 25.5 (8.3) was observed in the placebo cohort ($P < 0.05$). The decrease in mean Subscale C scores for patients with ADHD-CT was from 41.1 (7.9) at baseline to 29.8 (10.1) at visit 6 for the metadoxine ER group and from 40.9 (7.8) at baseline to 30.1 (13.2) at visit 6 for the placebo group ($P = 0.61$ [not significant (NS)]).

Mean (SD) CAARS-INV scores for Subscale A for patients with ADHD-PI decreased from 19.4 (4.5) at baseline to 10.3 (5.1) at visit 6 in the metadoxine ER cohort, and decreased from 20.7 (3.3) at baseline to 16.0 (5.4) at visit 6 in the placebo cohort ($P < 0.005$). Mean

Figure 1. Patient flow.



Abbreviations: AE, adverse event; ER, extended release; PI, principal investigator.

Figure 2. CAARS-INV score improvement from baseline to week 6, by ADHD subtype.

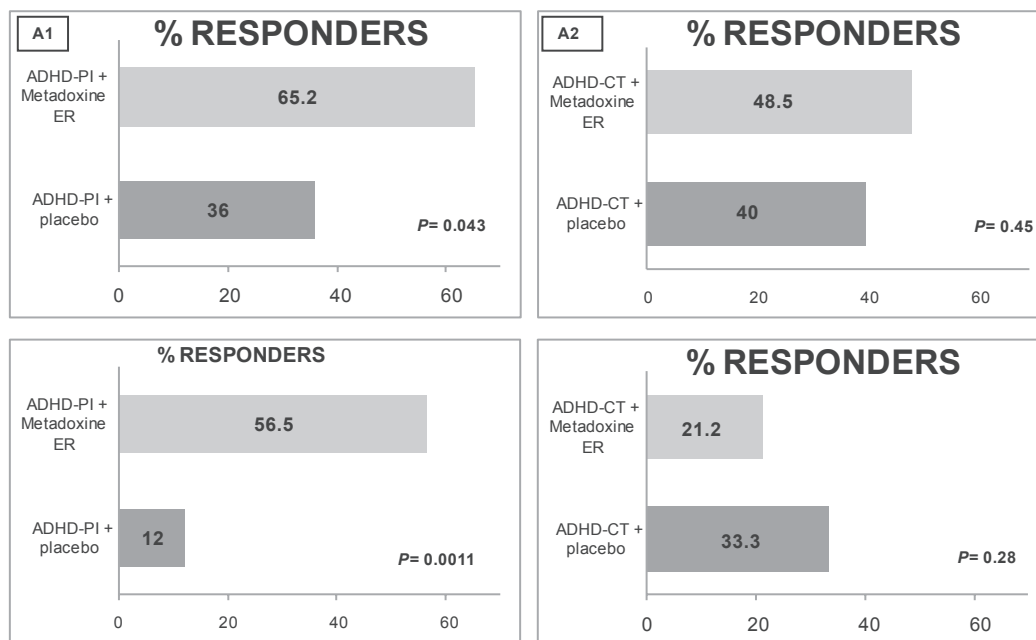
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CAARS-INV, Conners' Adult ADHD Rating Scale—Investigator Rated; CT, combined type; ER, extended release; PI, predominantly inattentive.

(SD) CAARS-INV scores for Subscale A for patients with ADHD-CT were not significantly different as a function of treatment (metadoxine ER cohort, 21.6 [4.1] at baseline vs 15.8 [6.0] at end of treatment; placebo cohort, 21.1 [3.9] at baseline vs 15.3 [6.7] at end of treatment; $P > 0.71$ [NS]).

Mean (SD) scores on Subscale B for patients with ADHD-PI decreased from 11.7 (4.4) at baseline to 7.3 (4.3) at visit 6 for the metadoxine ER group, and from 11.4 (5.8) at baseline to 9.5 (5.1) at visit 6 for the placebo group ($P > 0.20$ [NS]). Mean (SD) changes in Subscale B scores for patients with

ADHD-CT were from 19.6 (4.3) at baseline to 14.5 (6.1) for the metadoxine ER group, and from 19.8 (4.4) to 14.8 (7.1) for the placebo group ($P > 0.84$ [NS]).

The change in CAARS-INV scores for the entire sample from the screening visit to visit 6 was statistically significant for Subscale A ($P < 0.05$), but not significant for Subscale B ($P = 0.13$). When patients were analyzed by subtype, the change in CAARS-INV Subscale C score (ie, total score) was, again, statistically significant for patients with ADHD-PI ($P < 0.05$), but not significant for those with ADHD-CT ($P = 0.61$).

Figure 3. Clinical response rate as measured by a 25% (A1 and A2) and 40% (B1 and B2) decrease in CAARS-INV scores from baseline to week 6, by ADHD subtype.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CAARS-INV, Conners' Adult ADHD Rating Scale—Investigator Rated; CT, combined type; ER, extended release; PI, predominantly inattentive.

Secondary Outcomes

CAARS-INV Total ADHD Symptoms Score:

Response Rates

Figure 3 depicts 4 bar graphs showing the number of subjects who responded with a 25% and 40% decrease in CAARS-INV Subscale C scores from baseline according to ADHD subtype (ADHD-PI vs ADHD-CT).

In the ADHD-PI group, a $\geq 25\%$ improvement from baseline in CAARS-INV Total ADHD Symptoms score was shown at treatment endpoint in 65.2% of the patients taking metadoxine ER compared with 36.0% of those in the placebo group ($P = 0.04$, adjusted for baseline score, sex, site, and age using logistic regression). A $\geq 40\%$ improvement from baseline CAARS-INV Total ADHD Symptoms score was demonstrated at treatment endpoint in 56.5% of patients in the metadoxine ER group and 12.0% in the placebo group ($P = 0.001$).

In the ADHD-CT group, a $\geq 25\%$ improvement from baseline in CAARS-INV Total ADHD Symptoms score was shown at treatment endpoint in 48.5% of the patients taking metadoxine ER compared with 40.0% of those in the placebo group ($P = 0.45$ [NS]). A $\geq 40\%$ improvement from baseline in CAARS-INV Total ADHD Symptoms score was demonstrated at treatment endpoint in 21.2% of patients in the metadoxine ER group and 33.3% in the placebo group ($P = 0.28$ [NS]).

TOVA ADHD Scores

When subjects were divided by ADHD subtype, the changes in TOVA ADHD scores were only statistically significant in those subjects with ADHD-PI who were administered metadoxine ER compared with those administered placebo (Table 1).

In the ADHD-PI group, the change in TOVA ADHD score from baseline to week 1 differed significantly between patients taking metadoxine ER and those taking placebo ($P < 0.04$), as did the change from baseline to week 6 ($P < 0.05$) (Table 1). The TOVA ADHD scores among patients in the ADHD-CT group did not significantly differ when the drug and placebo groups were compared, and did not show the early response seen in the ADHD-PI group ($P = 0.74$ for change at week 1 and $P = 0.91$ for change at week 6).

AAQoL Scores

At screening, the mean AAQoL total scores were 58.4 and 56.3 in the metadoxine ER and placebo groups, respectively (Table 2). A mean increase of 10.9 points was observed in the metadoxine ER group between screening and the end of treatment (week 6), compared with 5.7 in the placebo group ($P < 0.01$ adjusted for baseline score, sex, site, and age). Subscale scores within the AAQoL also showed statistically significant differences between screening and end of treatment for those treated with metadoxine ER

Table 1. Changes in TOVAADHD Scores From Baseline to Week 1 (First Visit) and Week 6 (Last Visit) by ADHD Subtype for Metadoxine ER vs Placebo

		ADHD-PI Group (n = 48)				ADHD-CT Group (n = 65)			
		Change from baseline to week 1	P Value	Change from baseline to week 6	P Value	Change from baseline to week 1	P Value	Change from baseline to week 6	P Value
ADHD score	Metadoxine ER	4.79 (1.4)	< 0.04	6.70 (2.2)	< 0.05	2.10 (1.0)	0.74	3.82 (1.4)	0.91
	Placebo	1.74 (0.6)		2.78 (1.1)		2.51 (0.9)		2.60 (1.2)	
Errors of omission	Metadoxine ER	11.23 (5.3)	0.46	20.35 (6.2)	0.10	5.32 (4.4)	0.24	8.88 (4.2)	0.06
	Placebo	5.85 (4.0)		7.16 (4.9)		3.03 (3.8)		2.87 (5.1)	
Errors of commission	Metadoxine ER	13.23 (2.4)	< 0.04	15.39 (3.4)	0.60	9.24 (3.1)	0.20	11.70 (2.8)	0.20
	Placebo	5.58 (4.3)		13.08 (3.8)		10.52 (2.8)		12.30 (3.3)	
Response time	Metadoxine ER	-0.55 (3.3)	0.10	12.43 (2.9)	0.29	3.44 (3.0)	0.71	8.76 (3.3)	0.29
	Placebo	6.08 (2.7)		7.80 (3.6)		5.06 (2.8)		4.37 (3.8)	
Response time variability	Metadoxine ER	9.32 (4.6)	0.84	20.48 (4.7)	0.17	7.85 (3.5)	0.50	12.15 (5.0)	0.22
	Placebo	7.50 (3.3)		9.20 (5.4)		7.26 (3.6)		8.37 (3.7)	
D'	Metadoxine ER	16.77 (4.2)	0.40	24.83 (6.8)	0.13	6.76 (4.5)	0.23	11.88 (3.9)	0.17
	Placebo	6.65 (7.5)		9.40 (4.5)		4.48 (3.8)		2.97 (3.7)	

Data are presented as mean (standard deviation).

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; D', signal detection theory; CT, combined type; ER, extended release; PI, predominantly inattentive; TOVA, Test of Variables of Attention.

compared with placebo (all *P* values were adjusted for baseline score, sex, site, and age). These subscale scores included: 1) mean life productivity (*P* < 0.005); 2) mean psychological health (*P* < 0.005); and 3) mean relationships (*P* < 0.03). However, the life outlook score showed a nonsignificant improvement for both the metadoxine ER and placebo groups.

When separated according to ADHD subtype, there were no longer any significant findings for either subtype when evaluating the AAQoL Total score (*P* = 0.08 for patients with ADHD-PI; *P* = 0.10 for patients with ADHD-CT). The change from baseline to week 6 was statistically significant in favor of the metadoxine ER group over the placebo group with regard to the life productivity subscore in the ADHD-PI group (*P* = 0.01) and for the psychological health subscore in the ADHD-CT group (*P* = 0.01).

Adverse Events

Adverse events (AEs) for the entire cohort have been reported previously.²² The patients with ADHD-PI were significantly less likely to experience any AE during treatment with metadoxine ER (56.5%) than the cohort with ADHD-CT (88.2%) (Yates χ^2_1 , *P* = 0.02). However, in the placebo group, rates of AEs did not differ between patients with ADHD-PI (61.5%) and ADHD-CT (78.1%). For the subtype groups, regardless of treatment condition (ie, metadoxine ER or placebo), patients with ADHD-PI were significantly less likely to experience an AE (40.8%) compared with those with ADHD-CT (83.3%) (Yates χ^2_1 , *P* = 0.008).

Discussion

The first report from this study showed that a 6-week treatment period with oral metadoxine ER (1400 mg administered once daily without a titration period) resulted in a significant improvement in ADHD symptoms compared with placebo treatment.²² The secondary analyses reported here suggest that the ability of metadoxine ER to improve ADHD symptoms, TOVAADHD scores, and quality of life is most clearly seen in the PI subtype. The TOVAADHD scores were also significantly improved in patients with ADHD-PI who underwent treatment with metadoxine ER compared with those who took placebo. The differential findings of preferential effects of metadoxine ER versus placebo on patients with ADHD-PI versus those with ADHD-CT were not seen in AAQoL Total and subscale scores. Quality-of-life measures have not always improved temporally with ADHD symptom scores.²²

This finding of preferential effects on patients with ADHD-PI and IA symptoms with metadoxine ER is unique, as prior studies of use of stimulant and non-stimulant compounds in adults with ADHD have generally found similar effects on IA and H-I symptoms in the total ADHD sample, and equal effects in patients with PI and CT subtypes. Spencer et al³¹ found that dexamethylphenidate ER had equal effects on patients with PI and CT subtypes. A study of smoking cessation after treatment with osmotic-release oral system (OROS) methylphenidate versus treatment with placebo found that in heavy smokers, prolonged abstinence from smok-

Table 2. Changes in AAQoL Scores From Baseline to Week 6 by ADHD Subtype for Metadoxine ER vs Placebo

		ADHD (N = 110)		ADHD-PI (n = 48)		ADHD-CT (n = 62)	
		Change from baseline to week 6	P Value	Change from baseline to week 6	P Value	Change from baseline to week 6	P Value
AAQoL total score	Metadoxine ER	10.93 (1.5)	< 0.01	8.64 (2.2)	0.08	12.14 (2.0)	0.10
	Placebo	5.71 (2.1)		4.18 (3.1)		7.08 (3.1)	
Life productivity	Metadoxine ER	16.5 (1.8)	< 0.005	16.70 (2.5)	0.01	15.61 (2.4)	0.17
	Placebo	9.38 (2.4)		7.20 (3.6)		11.43 (3.4)	
Psychological health	Metadoxine ER	11.24 (2.3)	< 0.005	6.12 (3.8)	0.23	15.03 (2.8)	0.01
	Placebo	4.29 (2.7)		3.50 (3.5)		4.45 (4.1)	
Life outlook	Metadoxine ER	0.82 (1.9)	0.80	-1.79 (2.7)	0.58	2.18 (2.7)	0.96
	Placebo	2.07 (2.1)		1.12 (2.6)		3.02 (3.4)	
Relationships	Metadoxine ER	13.64 (2.3)	< 0.03	9.35 (3.5)	0.13	16.29 (3.1)	0.16
	Placebo	6.16 (2.9)		3.75 (4.7)		8.45 (3.6)	

Data are presented as mean (standard deviation).

Abbreviations: AAQoL, Adult ADHD Quality of Life; ADHD, attention-deficit/hyperactivity disorder; CT, combined type; ER, extended release; PI, predominantly inattentive.

ing was greater in patients with CT subtype who underwent OROS methylphenidate treatment than placebo treatment, while those with PI abstained from smoking longer with placebo treatment than with OROS methylphenidate.³² Large, placebo-controlled trials of treatment with the nonstimulant atomoxetine in adults with ADHD,³³ young adults with ADHD,³⁴ adults with ADHD and social anxiety disorder,³⁵ and adults with ADHD and alcohol substance use disorders³⁶ found equal effects on IA and HI symptoms. A pilot study of use of the amphetamine CX717 in adults with ADHD found greater effects on HI than on IA symptoms; however, another study of the amphetamine Org 26576 found equal effects on IA and HI symptoms.³⁷ Similarly, a multisite, placebo-controlled trial of the triple-beaded extended-release amphetamine SPD465³⁸ and an open-label trial of lisdexamfetamine³⁹ found equal effects on IA and HI symptoms.

In addition, the percentage of patients who achieved a $\geq 40\%$ improvement after placebo treatment was substantially greater in the ADHD-CT group than in the ADHD-PI group. Future placebo-controlled investigations into treatment effect on ADHD subtypes should evaluate potential differential effects in responder analyses after placebo treatment.

The findings of significant effects of metadoxine ER on the TOVA ADHD score in patients with ADHD-PI and not in those with ADHD-CT are consistent with the differential effects of the medication we observed on ADHD ratings with the CAARS-INV Subscale C scores. This finding is unique in the literature, as prior studies have generally found similar effects of treatment on TOVA ADHD scores in the different ADHD subtypes. For example, a study of children with ADHD found equal effects of methylphenidate on children with PI and CT subtypes.⁴⁰

The examination of AEs found that patients with ADHD-PI were less likely to experience AEs than those with ADHD-CT during treatment with metadoxine ER. It is not known if this subtype finding is specific to this trial of metadoxine ER and it should be examined in future studies of metadoxine, as well as other treatment studies in adults with ADHD.

Conclusion

These findings of potential preferential effects of metadoxine ER on adult patients with ADHD-PI and on IA symptoms of ADHD are of interest given the generally equivalent effects of ADHD treatments on IA and HI symptoms across ADHD subtypes reported in most other studies. This potential preferential effect on patients with ADHD-PI carries theoretical implications in terms of the validity of ADHD subtypes, validity of ADHD symptom factors, and possible differential neurobiological underpinnings of ADHD subtypes. The preferential effects on IA symptoms need to be replicated in subsequent studies to verify whether a differential effect is present.

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Conflict of Interest Statement

The Metadoxine Study Group includes Rachel Ben-Hayun, MD (Rambam Health Care Campus, Haifa); and Yaron Daniely, PhD, MBA (Alcobra, Ltd, Tel Aviv).

In the past year, Iris Manor, MD, has been a consultant to Enzymotec Ltd., Janssen-Cilag Israel, Teva Israel, Madison Israel, Novartis Israel, and Novartis International; and has been on a speakers/advisory board for Novartis International.

In the past year, Jeffrey H. Newcorn, MD, has received research support from Eli Lilly, Ortho-McNeil-Janssen, and Shire Pharmaceuticals. He also is or has been an advisor and/or consultant for Alcobra Ltd., BioBehavioral Diagnostics, Enzymotec Ltd., GencoSciences, Sunovion, and Shire Pharmaceuticals.

In the past year, Stephen V. Faraone, PhD, received consulting income and/or research support from Shire Pharmaceuticals, Akili Interactive Labs, VAYA Pharma, SynapDx, and Alcobra Ltd., and research support from the National Institutes of Health. His institution is seeking a patent for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received consulting fees, was on advisory boards, or participated in continuing medical education programs sponsored by: Shire Pharmaceuticals, Alcobra Ltd., Otsuka, McNeil, Janssen, Novartis, Pfizer Inc, and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health* and Oxford University Press: *Schizophrenia: The Facts*.

In the past year, Lenard A. Adler, MD, has been a consultant and on the advisory board to Alcobra Ltd., Shire Pharmaceuticals, Theravance, the National Football League, and Major League Baseball. He has also received research and grant support from Shire Pharmaceuticals, Chelsea Therapeutics, Department of Veterans Affairs Cooperative Studies, Theravance, and APSARD/Pont Foundation. Dr. Adler has also received royalty payments (as inventor) from New York University for license of adult ADHD scales and training materials since 2004.

Yaron Daniely, PhD, MBA, is an employee of Alcobra. Rachel Ben-Hayun, MD has been a consultant for Novartis and JC Healthcare in the last year.

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