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Placebo-Controlled Pilot Trial of Mecamylamine for Treatment of Autism Spectrum Disorders

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Abstract

Objective: To explore possible benefits of a nicotinic acetylcholine receptor (nAChR) agent for autistic symptoms based on postmortem observation of nAChR abnormalities (deficient $\alpha4\beta2$ nAChRs, excess $\alpha7$ nAChRs) in brains of patients with autism.

Method: Mecamylamine, because of its safety record in children with other disorders, was chosen for this first exploration. Twenty children with autism spectrum disorder age 4–12 years were randomly assigned for 14 weeks to placebo ($n=8$) or mecamylamine ($n=12$) in ascending fixed doses: 0.5 mg/day for 6 weeks, 2.5 mg for 2 weeks, then 5 mg/day for 6 weeks. Improvement was rated by a blinded independent evaluator. Because of small sample, data analysis was descriptive.

Results: Eighteen participants (10 mecamylamine, 8 placebo) completed the study. All doses were well tolerated; the only side effect of note was constipation (50% compared with 25% of placebo group). Three children had clinically nonsignificant electrocardiographic QT prolongation. Both groups showed modest to moderate improvement, but differences between groups were negligible. On the primary outcome measure, the Ohio Autism Clinical Impressions Scale, 90% of the active treatment group showed improvement at some point (but only 40% sustained it), compared with 62% on placebo. Of the four in active treatment that sustained improvement, three had a maximum dose of 0.13–0.15 mg/kg/day, while those who regressed had doses ≥ 0.18 mg/kg/day. Graphed means suggested better outcome with lower mg/kg and longer medication duration. Four parents spontaneously reported reduced hyperactivity and irritability and better verbalization and continued mecamylamine at their own expense.

Conclusion: Mecamylamine appeared to be safe, but not very effective in autism. The suggestion of better results at lower doses and longer exposure warrants consideration for future trials. The next step would be exploration of a more specific $\alpha4\beta2$ nAChR agonist, such as varenicline.

Introduction

Neuropathological data from autopsied basal forebrain have indicated an abnormality of the cholinergic system in autism (Bauman and Kemper 1994). Compared to age-matched individuals without autism, the brains of deceased people with autism have an extensive (60%–70%) loss of high-affinity nicotinic acetylcholine receptors (nAChRs) in the mesocortex (Perry et al. 2001). Studies based on radioligand binding autoradiography, protein subunit immunochemistry (western blotting), and messenger RNA quantitation (reverse transcription–polymerase chain reaction) indicate that the principal nAChR subtype involved is that containing the $\alpha4$ and $\beta2$ subunit combination. Neurochemical investigations of the cholinergic system in brain tissue have established an extensive loss of the $\alpha4\beta2$ nAChR subtype in cortical and cerebellar regions of adults with autism (Perry et al. 2001; Lee et al. 2002; Martin-Ruiz et al. 2004). This subtype is upregulated following the administration of nicotinic agonists such as nicotine in both human (Breese et al. 1997; Court et al. 1998; Perry et al. 1999) and animal models (Mochizuki et al. 1998; Sparks and Pauly 1999; Kassiou et al. 2001). Parallel neurochemical studies have identified loss of the $\alpha4\beta2$ nAChR in the cerebellum in autism that is similar to, but less extensive than that found in the cortex, and an increase in the $\alpha7$ nAChR subtype (Lee et al. 2002).

It is not yet clear whether and how extensively this nicotinic cholinergic abnormality relates to the clinical phenotype; however, nAChRs have generally been implicated in attention (Wesnes et al. 1983; Wesnes and Warburton 1984; Wesnes and Parrott 1992;

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Levin et al. 1998), learning (Levin 2002), anxiety (Picciotto et al. 2002), and pain perception (Marubio and Changeux 2000), which may all be relevant in autism. Perhaps more important for long-term treatment, the $\alpha4\beta2$ nAChR subtype has been implicated in neuroprotection and synaptic plasticity (McGehee 2002).

Two open label trials in children or adolescents with autism suggested that the cholinesterase inhibitor donepezil is of clinical benefit (Chez 2001; Hardan and Handen 2002). However, a controlled trial showed equivocal results (Handen et al. 2010, 2011). Cholinesterase inhibitors increase the level of acetylcholine and activate both muscarinic and nAChRs. However, nicotine, mecamylamine, and varenicline specifically target nAChRs. Nicotine has demonstrated efficacy and safety in placebo-controlled trials in children with Tourette's disorder (Silver et al. 2001a, 2001b), in placebo-controlled trials in adult attention-deficit/hyperactivity disorder (ADHD) (Conners et al., 1996) and in an open trial in adults age 20–30 years with Down syndrome (Bernert et al. 2001). The efficacy of nicotine in reducing inattention, hyperactivity, and irritability in other chronic disorders beginning in childhood, such as Down syndrome (Seidl et al. 2000; Bernert et al. 2001) and Tourette's disorder, supports the strategy of testing a nicotinic cholinergic agent in autism. Silver et al. (2001b) also reported an effect on mood; given the irritability and other associated mood problems often associated with autism spectrum disorders (ASDs), this provides further support for a hypothesized benefit in ASD.

Mecamylamine has clinical effects similar to nicotine in Tourette's disorder when used at low doses in combination with an antipsychotic drug (Silver et al. 2001b). Further, low doses of mecamylamine have been safely administered to a large number of children in a clinical trial in ADHD (Targacept, Inc., data on file). Extensive cardiac monitoring failed to show any change in cardiovascular functioning associated with daily exposures of mecamylamine up to 1.0 mg. The results of this trial failed to reach the level of significance on ratings of ADHD symptoms, but the safety of the drug in children at low doses was established. Further, Lipiello (2006) reported evidence supporting the hypothesis that normalization of cholinergic tone by selective antagonism of nAChRs may reduce the burden of core autism symptoms.

Many other neurotransmitter systems have been implicated one way or another in the etiology of autism (Lam et al. 2006). However, a nicotinic cholinergic abnormality may relate to other neurotransmitter anomalies in important ways. Reductions in hippocampal gamma-aminobutyric acid$_A$ ($GABA_A$) receptors (Blatt et al. 2001), glutamate decarboxylase (Fatemi et al. 2002), glutamate AMPA receptor, and glutamate transporter in the cerebellum (Purcell et al. 2001) implicate both GABA and glutamate. However, it is likely that there is a significant pathological link between the $\alpha4\beta2$ nAChR and GABA, so that nicotinic therapy may ameliorate dysfunctional GABA inhibition. Nicotinic receptors modulate GABA inhibition via both $\alpha4\beta2$ and $\alpha7$ nAChR subtypes (Alkondon and Albuquerque 2001).

Nicotine is traditionally considered to be an agonist and mecamylamine an antagonist. However, both drugs are associated with receptor desensitization. This indicates that in some respects, nicotine exerts a longer-term effect similar to an antagonist. Mecamylamine has a range of action across different doses, including cognitive enhancement (Mihailescu et al. 1998; Giniatullin et al. 2000; Buccafusco and Terry, 2002; Shytle et al. 2002).

An $\alpha4\beta2$ nAChR agonist would be a more intuitive nicotine-class drug to try in a pilot study, given the deficit of $\alpha4\beta2$ nAChRs documented in autism. For example, varenicline is an $\alpha4\beta2$ nAChR agonist and might be considered a more direct treatment of the $\alpha4\beta2$ nAChR deficiency, but its safety in children has not yet been established. The established safety of mecamylamine in studies of ADHD and Tourette's disorder made it a logical molecule to try first. Preliminary anecdotal clinical evidence suggested that in autistic patients, mecamylamine is associated with reduced compulsive behavior, improved social interaction and understanding, and more sophisticated conversation. Therefore we conservatively elected to try mecamylamine in this pilot trial.

Methods

Study design and treatment

This was a parallel-group, double-blind, placebo-controlled pilot trial of oral mecamylamine. Twenty children were randomly assigned in a ratio of 3:2 to receive mecamylamine (0.5 to 5.0 mg) or placebo. The acute phase of the trial lasted 14 weeks, followed by a 10-week open-label trial for placebo nonresponders. This pilot trial was funded by a grant through Autism Speaks. The Ohio State University Institutional Review Board approved the protocol and all parents/guardians provided written informed consent prior to participation.

Dosage started at 0.5 mg/day oral mecamylamine or matched placebo. Those who still had room for improvement and no limiting side effects at 6 weeks increased to 2.5 mg/day for 2 weeks and if still room for improvement and no limiting side effects at that dose, escalated to 5 mg/day for 6 weeks. Dose decreases to manage adverse effects were permitted at any time. Nonexclusionary background medications were continued as needed. Progress was monitored in clinical visits at the end of weeks 1, 2, 4, 6, 7, 8, 9, 10, 12, and 14.

Subjects

The subjects were 4 to 12 years of age, met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) criteria for Autistic Disorder or Pervasive Developmental Disorder Not Otherwise Specified based on clinical interview by a child psychiatrist and corroborated by the Autism Diagnostic Interview-Revised (ADI-R) by a research-certified administrator, and had an IQ of >36 or a mental age of >18 months. Exclusion criteria included the use of antipsychotic medications 3 months prior to baseline, psychoactive medications in the process of adjustment, systemic corticoids, or unstable seizure disorder. Subjects were also excluded if they began a major behavioral intervention within 2 months prior to baseline or planned to during the trial.

Assessments

Outcome measures included the Ohio Autism Clinical Impressions Scale (OACIS, Butter and Mulick 2006), the OSU Autism Rating Scale–DSM-IV (OARS-4; OSU RUPP 2005; http://psychmed.osu.edu/resources.htm#instruments), the Repetitive Behavior Scale (Bodfish et al. 1999), the Aberrant Behavior Checklist (Aman and Singh 1986, 1994), the Social Responsiveness Scale (Constantino et al. 2003), and target symptom assessment (Arnold et al. 2003). The OACIS was administered at every visit. The Repetitive Behavior Scale, Aberrant Behavior Checklist, and Social Responsiveness Scale were collected at baseline and every 2 weeks. The target symptom assessment was completed at baseline and weeks 2, 6, 8, 10, and 14. The OARS-4 was administered at baseline and weeks 6, 8, and 14.

In addition, cognition was assessed at baseline, weeks 6, 8, and end of treatment using a continuous performance task (Aman

1991), a cancellation task (Aman et al. 2008), and the Delayed Match-To-Sample Task (Aman and Turbott 1986; Aman 1991; Aman et al. 2003). Language was assessed at baseline and end of treatment using the Expressive Vocabulary Test-Second Edition (Williams 2007).

Safety assessments at screening/baseline and end point included physical exam, medical history, urinalysis, and for those able to cooperate, electrocardiogram, complete blood count (CBC), and blood chemistry. Vital signs, weight, and adverse events (AEs) were collected at each visit. A systematic side effects probe was also completed at every visit and concomitant medications were reviewed and recorded.

The OACIS-Improvement (OACIS-I, Butter and Mulick 2006), http://psychmed.osu.edu/resources.htm#instruments) is a 10-item clinician rated assessment designed to capture the clinician's global impression of the subject's improvement. The OACIS-I assesses improvement in social interaction, aberrant behavior, repetitive or ritualistic behavior, verbal communication, nonverbal communication skills, hyperactivity and inattention, anxiety and fearfulness, sensory sensitivities, restricted and narrow interests, and overall rating of autism. Each item is rated on a scale from 1 (*Very much improved*) through 4 (*No change*) to 7 (*Very much worse*). The OACIS-I was collected at every visit as the primary outcome measure. The main secondary measure was a z-score composite of all other scales.

The OARS-4 (OSU RUPP 2005), is a clinician-rated assessment based on a semi-structured interview with the subject's primary caregiver. Based on the DSM-IV symptoms of autistic disorder, it consists of 12 items rated from 0 (*Never or Rarely-Not a Problem*) to 3 (*Very Often-A Severe Problem*) comprising three subscales: (a) Impairment in social interaction, (b) Impairment in communication, and (c) Restricted, repetitive and stereotyped patterns of behavior, interests, and activities. It provides two summary scores: (a) A *weighted* score of severity of autism or autism spectrum symptoms (based on the 0–3 rating) and (b) A symptom count, based on how many symptoms received a rating >0. Each subscale symptom-count score can range from 0 to 4 with mean item scores ranging from 0.0 to 3.0.

Statistical methods

All subjects randomized were included in the analysis. The last-observation-carried-forward method was used to impute the missing data. The distribution of the subject baseline characteristics was compared across treatment groups. AEs were summarized by frequency counts and proportions. At each visit, pre-post change scores for all outcome measures were summarized by treatment groups using mean and standard deviation. Treatment effect size for all the outcome measures and the combined z-score was reported for visit week 14 only. Although we did not expect statistical

Table 1. Sample Characteristics (n = 20)

	Placebo (n = *8*)	*Active* (n = *12*)	*Total* (n = *20*)
Age (year), mean, ± SD	8.36, ± 2.83	6.76, ± 2.24	7.40, ± 2.55
Weight (kg), mean, ± SD	40.26, ± 20.69	26.68, ± 7.83	32.40, ± 15.75
Height (cm), mean, ± SD	131.31, ± 19.61	122.14, ± 13.61	126, ± 16.56
Gender			
Male, *n* (%)	6 (75)	11 (91.67)	17 (85)
Female, *n* (%)	2 (25)	1 (8.33)	3 (15)
Race			
White, *n* (%)	8 (100)	9 (75)	17 (85)
Asian, *n* (%)	0 (0)	2 (16.67)	2 (10)
Other, *n* (%)	0 (0)	1 (8.33)	1 (5)
Diagnosis			
Autistic disorder, *n* (%)	7 (87.5)	10 (83.33)	17 (85)
PDD-NOS, *n* (%)	1 (12.5)	2 (16.67)	3 (15)
IQ[a], mean, ± SD	62.62, ± 32.53	77.58, ± 21.12	71.60, ± 26.55
IQ range (mean)	17–124 (107)	37–113 (76)	17–124 (107)
Entry OACIS-S score, mean, ± SD	5.38, ± 0.92	5.25, ± 0.75	5.3, ± 0.80
Entry SRS total score, mean, ± SD	120.63, ± 30.55	95.08, ± 19.72	105.30, ± 27.09
Entry RBS total score, mean, ± SD	38.38, ± 20.16	29.42, ± 15.81	33, ± 17.74
Entry ABC scores:			
Irritability, mean, ± SD	12.88, ± 9.60	12.75, ± 9.42	12.80, ± 9.24
Lethargy, mean, ± SD	17.00, ± 9.37	10.33, ± 6.46	13.00, ± 8.23
Stereotypy, mean, ± SD	9.75, ± 6.25	4.25, ± 3.60	6.45, ± 5.43
Hyperactivity, mean, ± SD	19.13, ± 13.02	21.17, ± 11.71	20.35, ± 11.95
Inappropriate Speech, mean, ± SD	4.63, ± 3.20	4.50, ± 3.73	4.55, ± 3.44
Entry ADI-R Subscale A-Reciprocal Social Interaction, mean, ± SD	26.63, ± 5.80	23.00, ± 5.56	24.4, ± 5.80
Entry ADI-R Subscale B-Communication, mean, ± SD	16.25, ± 3.77	13.17, ± 3.93	14.40, ± 4.07
Entry ADI-R Subscale C-Restricted, Repetitive, and Stereotyped Patterns of Behavior, mean, ± SD	7.00, ± 2.07	4.92, ± 1.73	5.75, ± 2.10

[a]This study utilized the Stanford Binet 5 (5 participants), the Leiter-R (13 participants), and the Mullen Early Scales of Learning (2 participants).

SD = standard deviation; PDD-NOS = Pervasive Developmental Disorder-Not Otherwise Specified; OACIS-S = Ohio Autism Clinical Global Impressions Scale-Severity; SRS = Social Responsiveness Scale; RBS = Repetitive Behavior Scale; ABC = Aberrant Behavior Checklist; ADI-R = Autism Diagnostic Interview-Revised.

significance at this sample size, Fisher's exact test was used to analyze the categorical variables. For continuous variables, *p*-values were calculated based on Wilcoxon ranked sum test. Simple linear regression was used to examine the relationship between the dose or weight and the mean OACIS item.

Results

Twenty children were randomized, 8 to placebo and 12 to active mecamylamine. Demographic and clinical characteristics of the 20 participants are presented in Table 1. At study entry, the placebo group had higher scores on: Aberrant Behavior Checklist (ABC) Stereotypy subscale ($p=0.05$), ADI-R Restricted, Repetitive, and Stereotyped Patterns of Behavior score ($p=0.03$), and Social Responsiveness Scale total ($p=0.04$). No significant differences were found for age, weight, sex, diagnosis, IQ, or entry scores for the OACIS, RBS, ABC Irritability, ABC Hyperactivity, ABC Lethargy/Social Withdrawal, ABC Inappropriate Speech, ADI-R Qualitative Abnormalities in Reciprocal Social Interaction or ADI-R Qualitative Abnormalities in Communication.

Two of those in active treatment dropped out after 4 weeks with lack of improvement; in one case the child had stopped psychoactive medication to enter the study and had deteriorated to an intolerable extent. In the other case the family moved to an inconvenient distance. Their termination assessments were carried forward in the data analysis. The remaining 18 (10 mecamylamine, 8 placebo) finished the full 14 weeks of double-blind treatment, using all doses. No dose reduction for AEs was needed, but in one case after study completion the parents and physician decided that the child had done better with the middle dose than the high dose.

No statistically or clinically significant difference in the amount of improvement was seen between placebo and mecamylamine on any measure (Table 2a, b), except one subscale of the Social Responsiveness Scale on which placebo did better than active mecamylamine. In the active treatment group, nine (90% of the completers) showed some improvement on the OACIS-I overall score (rating < 4) at some point (but only four sustained that improvement after escalating to the highest dose), compared with five (62%) in the placebo group showing improvement at some point.

Of the four children in the active treatment group who sustained improvement through end point, three (75%) had a maximum dose between 0.13 and 0.15 mg/kg/day, while the remaining participants received doses of 0.18 mg/kg/day or more. The relationship among mg/kg/day dose, size of child, and duration of exposure is illustrated in Figure 1. Note that the OACIS-I score tends to be better at lower mg/kg/day doses, higher body weight, and longer duration of exposure. Unfortunately, duration is confounded with dose in the fixed escalation, but it appears that increased dose cannot explain the better response at 14 weeks because the response is inverse to the mg/kg/day dose.

Safety measures

Table 3 shows AEs, including worsening of pre-existing conditions. Except for constipation, which occurred twice as often in the mecamylamine group as in placebo, the treatment groups were not different. Additionally, some AEs that were expected side effects, such as blurred vision and urinary retention, were not reported by any participants. No AE required dosage reduction.

Physical exams at end point showed no new pathology except for one instance of pneumonia, which was judged not to be related to study treatment. One child had a ''sticky heart valve''

TABLE 2A. GLOBAL OUTCOME MEASURES BY TREATMENT GROUP AND TIME

	Placebo				*Active mecamylamine*				
	BL	*Change week 6*	*Change week 8*	*Change week 14*	*BL*	*Change week 6*	*Change week 8*	*Change week 14*	*ES (p) of group difference*[a]
OACIS-S									
Overall autism	5.63 ± 0.74	−0.25 ± 0.46	−0.38 ± 0.52	−0.63 ± 0.74	5.25 ± 0.75	−0.17 ± 0.41	−0.33 ± 0.49	−0.58 ± 0.79	−0.05 (0.91)
Noncore items	4.00 ± 1.13	−0.13 ± 0.35	−0.42 ± 0.68	−0.38 ± 0.58	3.53 + 1.17	−0.11 ± 0.33	−0.22 ± 0.48	−0.28 ± 0.72	−0.15 (0.75)
Autism symptoms	5.20 ± 0.93	−0.14 ± 0.28	−0.41 ± 0.41	−0.52 ± 0.52	4.70 ± 0.60	−0.21 ± 0.30	−0.37 ± 0.45	−0.49 ± 0.50	−0.06 (0.90)
OACIS-I									
Overall autism	4.00[b]	−0.38 ± 0.52	−0.63 ± 0.74	−0.88 ± 0.64	4.00[b]	−0.50 ± 0.52	−0.58 ± 0.51	−0.92 ± 0.79	0.06 (0.90)
Noncore items	4.00[b]	−0.13 ± 0.56	−0.46 ± 0.73	−0.38 ± 0.72	4.00[b]	−0.17 ± 0.58	−0.31 ± 0.63	−0.25 ± 0.75	−0.17 (0.72)
Autism symptoms	4.00[b]	−0.27 ± 0.37	−0.50 ± 0.53	−0.71 ± 0.55	4.00[b]	−0.37 ± 0.29	−0.49 ± 0.41	−0.68 ± 0.59	−0.06 (0.90)
OARS									
Total impairment	2.06 ± 0.45	−0.09 ± 0.21	−0.13 ± 0.21	−0.32 ± 0.34	1.83 ± 0.42	−0.16 ± 0.26	−0.25 ± 0.31	−0.30 ± 0.33	−0.07 (0.89)
No. of symptoms	10.5 ± 1.07	0.13 ± 0.35	0.13 ± 0.35	0 ± 0.53	10.08 ± 1.16	0.08 ± 0.29	0.08 ± 0.29	−0.25 ± 0.45	0.51 (0.27)
Target symptoms	5.00[b]	−0.73 ± 0.96	−1.33 ± 0.87	−1.56 ± 1.05	5.00[b]	−0.69 ± 0.78	−1.10 ± 1.08	−1.46 ± 1.38	−0.08 (0.86)
Z Score[c] composite	0.38 ± 0.99	−0.32 ± 0.56	−0.61 ± 0.73	−0.73 ± 0.90	−0.25 ± 0.70	−0.44 ± 0.60	−0.59 ± 0.64	−0.62 ± 0.71	−0.14 (0.76)

[a]Negative ES (Cohen's d) reflects placebo showing nominally more improvement than active mecamylamine.
[b]Baseline for OACIS-I is 4 by definition, and baseline for Target Symptoms is 5 by definition; Therefore sd is 0 and meaningless.
[c]Mean of Z scores from all scales (including Table 2B) based on baseline means and SD.
Lower scores are better on all measures.
BL = baseline; ES = effect size; OACIS-I = Ohio Autism Clinical Impressions Scale-Improvement; OARS = OSU Autism Rating Scale.

Table 2B. Specific Outcome Measures by Treatment Group and Time

	Placebo				*Active*				
	BL	*Change week 6*	*Change week 8*	*Change week 14*	*BL*	*Change week 6*	*Change week 8*	*Change week 14*	*ES (p) of group difference*[a]
Aberrant Behavior Checklist									
Irritability	12.88 ± 9.60	−3.63 ± 10.06	−5.25 ± 10.04	−5.00 ± 10.78	12.75 ± 9.42	−3.08 ± 7.24	−5.50 ± 7.50	−3.17 ± 8.76	−0.19 (0.68)
Lethargy	17.00 ± 9.37	−4.13 ± 7.53	−6.38 ± 8.72	−7.50 ± 9.56	10.42 ± 6.61	−4.5 ± 6.68	−5.00 ± 7.86	−4.25 ± 6.97	−0.40 (0.39)
Stereotype	9.75 ± 6.25	−0.63 ± 4.78	−2.38 ± 5.66	−1.63 ± 7.11	4.17 ± 3.54	−1.25 ± 3.08	−2.00 ± 2.26	−1.42 ± 2.64	−0.04 (0.93)
Hyperactivity	19.13 ± 13.02	−4.63 ± 10.91	−4.88 ± 12.47	−5.50 ± 12.06	21.08 ± 11.74	−6.67 ± 10.87	−6.75 ± 10.55	−6.92 ± 11.25	0.12 (0.79)
Inappropriate speech	4.38 ± 3.16	−0.5 ± 2.00	−1.13 ± 2.42	−1.75 ± 2.38	4.50 ± 3.73	−1.58 ± 2.78	−1.92 ± 2.02	−1.50 ± 3.90	−0.07 (0.87)
Repetitive Behavior Scale									
Stereotypy	7.38 ± 3.16	−0.88 ± 4.64	−2.13 ± 4.22	−0.63 ± 6.21	4.58 ± 2.87	−1.67 ± 2.93	−1.83 ± 2.62	−1.92 ± 2.94	0.29 (0.54)
Self-injury	4.50 ± 3.82	−1.75 ± 4.20	−2.00 ± 3.96	−2.88 ± 4.39	1.75 ± 2.01	−0.33 ± 1.56	−0.25 ± 2.01	−0.83 ± 1.53	−0.68 (0.15)
Compulsive	7.25 ± 4.53	−2.63 ± 2.56	−3.75 ± 2.49	−3.50 ± 3.38	5.50 ± 3.90	−2.83 ± 3.83	−3.25 ± 3.25	−2.42 ± 3.55	−0.31 (0.50)
Ritualistic	5.88 ± 4.91	−0.38 ± 2.26	−2.13 ± 3.40	−2.00 ± 3.02	6.00 ± 4.63	−1.75 ± 4.25	−2.42 ± 3.99	−1.75 ± 4.58	−0.06 (0.89)
Sameness	9.38 ± 6.14	−1.25 ± 3.77	−2.75 ± 4.53	−2.50 ± 3.21	8.08 ± 5.62	−4.00 ± 5.94	−3.92 ± 6.26	−4.67 ± 6.05	0.42 (0.37)
Restricted	4.13 ± 2.75	−1.00 ± 2.93	−1.25 ± 2.82	−1.13 ± 2.64	3.92 ± 3.23	−2.00 ± 2.22	−1.92 ± 2.27	−1.58 ± 2.50	0.18 (0.70)
Social Responsiveness Scale									
Receptive	16.38 ± 2.62	−0.63 ± 2.13	−2.25 ± 3.41	−2.25 ± 3.06	11.92 ± 2.64	0.25 ± 2.05	0 ± 1.95	0.33 ± 1.78	−1.10 (0.03)
Cognitive	22.75 ± 6.04	−0.88 ± 2.23	−2.63 ± 6.67	−2.13 ± 5.74	19.50 ± 2.88	−1.67 ± 4.85	−1.67 ± 4.68	−2.50 ± 5.39	0.07 (0.88)
Expressive	39.88 ± 11.68	−3.00 ± 6.68	−6.63 ± 10.77	−7.25 ± 8.55	34.33 ± 8.14	−2.00 ± 7.83	−3.75 ± 7.74	−4.17 ± 7.31	−0.39 (0.40)
Motivation	19.13 ± 4.26	−1.38 ± 2.45	−4.25 ± 5.57	−5.75 ± 4.89	13.00 ± 4.69	−2.92 ± 4.78	−3.50 ± 4.56	−3.83 ± 4.55	−0.41 (0.38)
Preoccupations	22.50 ± 7.67	−2.00 ± 4.81	−4.50 ± 5.45	−4.88 ± 6.92	16.33 ± 6.88	−1.75 ± 7.82	−2.92 ± 7.42	−3.33 ± 7.43	−0.21 (0.65)
EVT	47.5 ± 24.74	—	—	0 ± 6.42	74.0 ± 16.34	—	—	−2.14 ± 10.12	0.25 (0.66)

[a]Negative effect size (ES, Cohen's d) reflects more improvement in placebo group except for EVT, for which positive ES reflects more improvement in placebo.
EVT = Expressive Vocabulary Test. The *n* for this measure is 13 (6 placebo and 7 active). This measure was only collected at baseline and end point.
BL = baseline; ES = effective size.

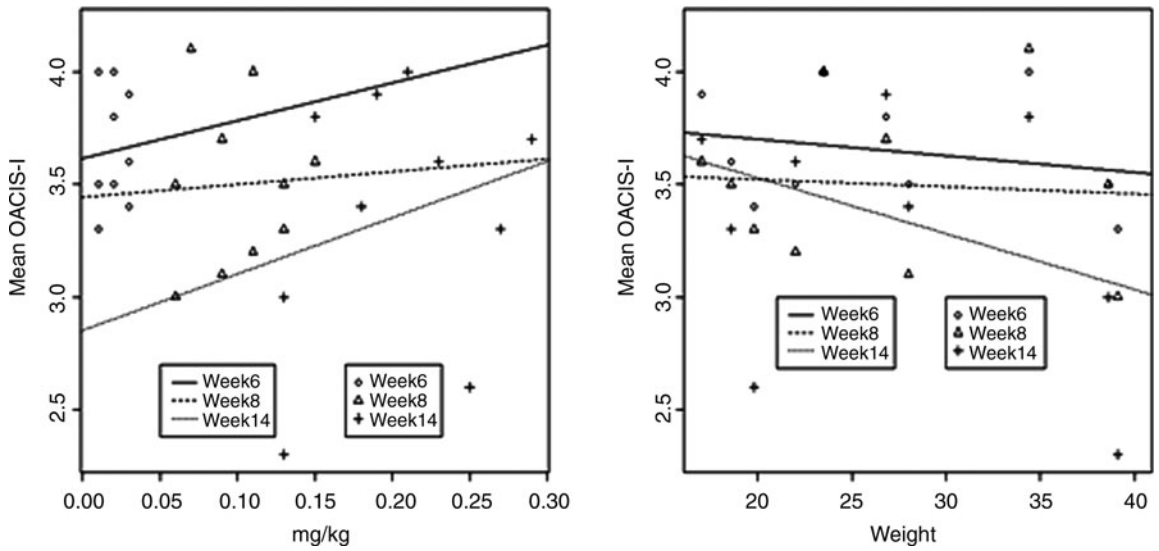

FIG. 1. Ohio Autism Clinical Impressions Scale-I (OACIS-I) Item Mean by Dose, Duration, and Weight. Lower score is better. Week 6 = 0.5 mg/day; week 8 = 2.5 mg/day; week 14 = 5 mg/day. Left panel: Lower mg/kg dose and longer duration are associated with better outcome. Better result at 14 weeks could be higher dose or longer duration of dosing because dose and duration are confounded, but duration seems the most likely association in view of the better outcome at lower mg/kg doses. Right panel: Association of better outcome with higher body weight (resulting in lower mg/kg doses in this fixed-dose titration). Results are not statistically significant at this sample size.

diagnosed in infancy and followed up by a cardiologist, with no worsening during the study. Vital signs, of particular interest given that mecamylamine was originally used as an antihypertensive medication, were unremarkable. The mean heart rate for the treatment group at baseline, 6, 8, and 12 weeks (respectively, in beats per minute) was 98, 96, 98, and 102, compared with 100, 103, 103, and 93 for placebo. The mean blood pressure (systolic/diastolic, in mm Hg) for baseline, 6, 8, and 12 weeks in the treatment group were 99/64, 96/64, 100/65, and 105/70, compared with 107/69, 105/65, 102/66, and 106/62 for placebo.

Electrocardiograms (ECGs) were successfully collected at screen and end point from 15 children (nine active and six placebo); the other five could not cooperate with ECG. The readings were generally normal with some exceptions; one child developed prolonged QT interval, another developed borderline QT interval, and a third went from borderline QT interval at screen to frank prolonged QT at end point. No physical signs or symptoms were associated with these ECG changes. Two children with previously diagnosed cardiac pathology (right atrial enlargement and valvular stenosis with left ventricular hypertrophy) were cleared for study participation by their cardiologists and experienced no exacerbation of these conditions during the study.

Urinalysis was obtained at screen and end point for 15 children (eight active and seven placebo) and blood chemistries and CBCs were obtained at screen and end point on 16 children (nine active and seven placebo); the remainder declined to cooperate. Lab values generally showed no change from screen to week 14. Six children (two active and four placebo) had abnormal lipids at screen; in three of these cases, abnormally high LDL cholesterol improved by 19 (placebo), 21 (placebo), and 21(active) points, respectively. No child showed new lipid abnormalities or worsening at 14 weeks. Other labs were unremarkable.

As one way of reducing the number of statistical tests while harnessing the multiple outcome measures incorporated, we constructed standard scores based on the principle clinical assessments of interest. The analysis for this z-score composite appears in the last line of Table 2a and is not significant.

Table 3. Summary of Adverse Events by Treatment Groups on the Checklist of Expected Side Effects

Adverse event checklist	*Placebo* (n = *8*) n *(% of group)*	*Active treatment* (n = *12*) n *(% of group)*
Constipation	2 (25%)	6 (50%)
Vomiting/nausea	3 (37.5%)	3 (25%)
Anorexia	5 (62.5%)	4 (33%)
Dry mouth	1 (12.5%)	1 (8%)
Mental symptoms	4 (50%)	6 (50%)
Sedation	2 (25%)	1 (8%)
Lung congestion	6 (75%)	9 (75%)
Urinary retention	0 (0%)	0 (0%)
Blurred vision	0 (0%)	0 (0%)
Dilated pupils	1 (12.5%)	1 (8%)
Weakness	2 (25%)	2 (16%)
Fatigue	3 (37.5%)	4 (33%)

Discussion

Anecdotally, there were four cases in which parents reported enough improvement that they chose to continue the mecamylamine after the study. In each of those cases, the parents stated that they noticed the greatest improvement in their child's irritability and hyperactivity, but also mentioned increased verbalization. The improved irritability would be compatible with the mood improvements reported by Silver et al. (2001b). However, these anecdotal improvements were not confirmed on a group basis by ABC irritability or hyperactivity scores or by Expressive Vocabulary Test (Table 2b). Nevertheless, the possibility of mood improvement may deserve further exploration.

Although mecamylamine appears safe for children with autism (despite three cases of clinically nonsignificant QT prolongation),

the results of this pilot trial did not suggest clinically (or statistically) significant benefit on a group basis. Qualitative examination of the data suggested that improvement was greatest and was most likely to be sustained when the maximum daily dose was between 0.13 and 0.15 mg/kg. Possible reasons for failing to find benefit in the whole sample could be wrong dose or duration, restriction of benefit to a small minority, or simply that this medication is not useful in ASD. In view of the slightly better results at lower mg/kg/day dosage and at 14 weeks despite the absolute doses being higher at 14 weeks, the dosage and duration issues may deserve further exploration. Such exploration would need to monitor ECGs in view of the three cases with QT prolongation, which may be avoided by lower doses. However, those descriptive dose and duration impressions are limited by the small sample size.

Limitations

The most obvious limitation of this pilot trial is its small sample size spread over a large age range. Another is the confounding of dose with duration of treatment. Also, there was no attempt to sculpt doses to body size (other than clinical titration). In retrospect a dose-finding study prior to a placebo-controlled trial may have been useful.

Conclusions

Although it made sense to explore mecamylamine first because of its previous safety record in children, varenicline is more likely to address the specific $\alpha4\beta2$ nAChR deficiency hypothesis, as it is a specific partial agonist of $\alpha4\beta2$ nAChR. The response to mecamylamine was disappointing but not surprising, given that it does not particularly target the $\alpha4\beta2$ nAChR. The next logical step may be to turn interest to a nicotinic agent with more $\alpha4\beta2$ affinity. A cautious trial of varenicline or other $\alpha4\beta2$ nAChR agonist may be the most rational extension of this trial (Deutsch et al. 2010; Anand et al. 2011).

Clinical Significance

These results are of most use to investigators. It appears that a second placebo-controlled trial of mecamylamine at a dose of 0.13–0.15 mg/kg/day for 3 months might be useful, although it would appear that resources might be better devoted to a trial of an $\alpha4\beta2$ nAChR agonist. As it stands, the use of mecamylamine in children with autism would be off-label and without evidence of efficacy. If a clinician feels an individual trial is indicated for a child with hyperactivity and irritability unresponsive to the Food and Drug Administration-approved drugs, the dose most likely to help would be below 0.15 mg/kg/day maintained for several months. In view of the slight prolonging of QT interval, ECG monitoring would be desirable.

Disclosures

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