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An Open-Label Naturalistic Pilot Study of Acamprosate in Youth with Autistic Disorder

Craig A. Erickson, M.D., Maureen Early, B.S., Kimberly A. Stigler, M.D., Logan K. Wink, M.D., Jennifer E. Mullett, R.N., B.C., and Christopher J. McDougle, M.D.

Abstract

To date, placebo-controlled drug trials targeting the core social impairment of autistic disorder (autism) have had uniformly negative results. Given this, the search for new potentially novel agents targeting the core social impairment of autism continues. Acamprosate is U.S. Food and Drug Administration–approved drug to treat alcohol dependence. The drug likely impacts both gamma-aminobutyric acid and glutamate neurotransmission. This study describes our initial open-label experience with acamprosate targeting social impairment in youth with autism. In this naturalistic report, five of six youth (mean age, 9.5 years) were judged treatment responders to acamprosate (mean dose 1,110 mg/day) over 10 to 30 weeks (mean duration, 20 weeks) of treatment. Acamprosate was well tolerated with only mild gastrointestinal adverse effects noted in three (50%) subjects.

Introduction

The central impairment in autistic disorder (autism) is a marked disturbance in social relatedness. Kanner (1943) in his first classic work on autism described this as an ''innate inability to form the usual, biologically provided affective contact with people.'' This core social impairment is lifelong and as such contributes significantly to the burden of autism on the individual, family, and society.

The heterogeneous clinical presentation of autism, combined with disparate neurochemical and genetic findings, has limited treatment development for core social impairment. Many symptoms commonly seen in autism, including inattention, hyperactivity, irritability, aggression, and insomnia, are generally agreed upon to often be responsive to drug treatment (Posey and McDougle 2000). To date, controlled drug trials targeting the core social deficits of autism have yielded uniformly negative results. These include negative trials of fenfluramine (Campbell et al. 1988; Posey et al. 2008), naltrexone (Campbell et al. 1993), lamotrigine (Belsito et al. 2001), donepezil (Chez et al. 2003), secretin (Sturmey 2005), and D-cycloserine (Posey et al. 2008). The lack of successful drug development focused on social impairment is striking given the centrality of these symptoms and the resultant significant lifelong morbidity.

Acamprosate, a U.S. Food and Drug Administration–approved drug for the maintenance of abstinence from alcohol use in adults, is a novel agent with multiple mechanisms of action. Acamprosate has been demonstrated to bind at a specific spermidine-sensitive site at the N-methyl-D-aspartate (NMDA) glutamate receptor (Naassila et al. 1998; Mayer et al. 2002). It has complex actions at NMDA receptors: enhancing activation at low glutamate concentrations and inhibiting receptor activation at high glutamate concentrations when the receptors are most active (Naassila et al. 1998; Mayer et al. 2002). This mechanism may underlie the positive impact of acamprosate on alcohol withdrawal, a state characterized by excess NMDA receptor activation producing symptoms such as delirium tremens and seizures (Mason and Heyser 2010). Acamprosate has recently been demonstrated to act as an antagonist at metabotropic glutamate receptors (mGluRs). The drug also blocks the neurotoxic effects of the mGluR agonist trans-ACPD (Harris et al. 2002).

Acamprosate has also been specifically linked to antagonism at the mGluR type 5 (mGluR5) neuroreceptor. Acamprosate and the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) both have been associated with increased sedative effects of alcohol and reduced alcohol withdrawal in mice; no effects of acamprosate or MPEP were noted in mGluR5 knockout mice (Blednov and Adron Harris 2008). Gupta et al. (2008) demonstrated that acamprosate and MPEP both dose dependently reduced ethanol drinking in the drinking-in-the-dark mouse model. In mice, acamprosate and the mGluR5 antagonist (2-methyl-1,3-thiazol-4-yl) ethynyl pyridine were associated with reduction of alcohol withdrawal-associated anxiety effects as observed by increased time spent and entry into the open arms of a maze with acamprosate treatment (Kotlinska and Bochenski 2008). In other animal studies acamprosate has been shown to act as an agonist at gamma-aminobutyric acid (GABA) type A (GABA(A)) neuroreceptors (Pierrefiche et al. 2004; Mann et al. 2008). In neonatal rat brain stem slices,

Department of Psychiatry, Christian Sarkine Autism Treatment Center, Indiana University School of Medicine, James Whitcomb Riley Hospital for Children, Indianapolis, Indiana.

acamprosate induced neuronal inhibitory effects mediated by an increase in GABA(A) activity (Pierrefiche et al. 2004).

In many instances, significant overlap exists between the potential pharmacodynamic mechanisms of acamprosate and abnormalities noted in studies of the pathophysiology of autism. A review of glutamatergic and GABAergic function in autism reveals this overlap, which supports the potential utility of acamprosate as a candidate drug for targeting core deficits in autism.

Glutamatergic dysregulation has been consistently found in autism (Erickson et al. 2008). Peripheral glutamate has been shown to be increased in youth (Aldred et al. 2003) and adults (Shinohe et al. 2006) with autism compared with controls. In postmortem analysis, cortical glutamic acid decarboxylase (GAD) protein levels were reduced (Fatemi et al. 2002). GAD is responsible for converting glutamate to GABA, thus pointing to the potential for an imbalance between excessive glutamate and reduced GABA activity in autism. Also, in postmortem specimens, NMDA receptor 1 protein levels were increased in the cerebellar tissue of persons with autism (Purcell et al. 2001). Magnetic resonance spectroscopy has noted increased glutamate and glutamine concentrations in the amygdala-hippocampal region in persons with autism compared with controls (Page et al. 2006). Genetic studies in autism have implicated a number of rare gene alterations implicated in glutamatergic function. Those include neurexins, which via neuroligans induce presynaptic differentiation of glutamatergic neurons, ionotropic kainite receptor 6, and mGluR 8 (for review see Erickson et al. 2008). Several recent drug trials in autism have focused on drugs impacting glutamate neurotransmission. Open-label reports have described use of the NMDA receptor antagonist memantine. Our group completed an open-label memantine trial (mean dose, 10.1 mg/day) in 18 youth with pervasive developmental disorders (PDDs) (Erickson et al. 2007). Clinical improvement was noted in 11 subjects (61%) with change noted in a number of behaviors, including inattention and social withdrawal.

GABA dysfunction, specifically at the GABA(A) receptor, has been implicated in the pathophysiology of autism. Single-nucleotide polymorphisms in the GABA(A) receptor subunit genes *GABRB3*, *GABRA5*, and *GABRG3* have been identified (Menold et al. 2001; Kim et al. 2006; Delahanty et al. 2011). The GABA(A) receptor genes are located in chromosome region 15q11-13, a region frequently implicated in the pathogenesis of autism. GABRB3 knockout mouse models of autism show impairments in social relatedness and attention (DeLorey 2005). In human brain samples, GABA(A) receptor subunits are underexpressed compared to control specimens (Hogart et al. 2007; Fatemi et al. 2009). GABA(A) receptor genes are normally biallelically expressed in human brain, but were biallelically expressed in only 4 of 8 brain specimens from persons with autism, indicating potential epigenetic dysregulation of these genes (Hogart et al. 2007).

Use of acamprosate in three adults with fragile X syndrome (FXS) and comorbid PDDs was recently described (Erickson et al. 2010). In this report, acamprosate use (333–1,998 mg/day) over 16–28 weeks was associated with improvement in social behavior and communication. Two individuals developed mild emesis during treatment and one individual experienced sedation. FXS is the most common single-gene cause of autism. Excess activity at mGluR5 receptors has been implicated in the pathophysiology of FXS (Bear et al. 2004).

Overall, significant overlap exists between biological systems potentially dysregulated in autism and systems implicated in the pharmacodynamic profile of acamprosate. This overlap, combined with an initial report of treatment response in FXS, provides the theoretical foundation for consideration of use of acamprosate targeting the core social impairment of idiopathic autism. With this in mind, we completed a naturalistic open-label trial of acamprosate in youth with autism targeting core social impairment.

Methods

Design

This naturalistic open-label trial prospectively followed the clinical treatment of the first six youth with autistic disorder who received acamprosate (minimum dose 333 mg/day) for at least 4 weeks. This study was approved by our local Institutional Review Board and written consent for treatment was obtained in all cases.

Subjects

Six subjects (mean age 9.5 years; range 6–12.5 years) meeting diagnostic criteria for autistic disorder based upon *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV TR) (American Psychiatric Association 2000) were enrolled in the study. Potential subjects with significant comorbid psychiatric (e.g., psychotic or mood disorders) and medical (e.g., active seizure disorder) conditions were excluded from the study. Concomitant psychotropic drug use was allowed with stable dosing for at least 8 weeks before the trial. Exceptions included glutamatergic agents such as memantine, riluzole, and D-cycloserine. All subjects were able to complete a minimum of 4 weeks of treatment and tolerate a minimum dose of 333 mg/day of acamprosate.

Treatment

Acamprosate is commercially available in 333 mg enteric-coated pills. Subjects were started on 333 mg/day with dose increases every other week by this amount up to a maximum dosing of 1,332 mg/day, divided three times daily. Dose titration was halted if significant positive clinical change was noted or if intolerable adverse effects developed. Follow-up phone calls to make dose adjustments, based upon clinical response and adverse effects, occurred every 2 weeks before the first initial follow-up appointment after 8 weeks of treatment. Subsequent follow-up visits occurred in 8–12 week intervals.

Measures

All ratings were done at baseline, at 8 weeks, and at last clinical visit. The primary clinician-rated measures included the Clinical Global Impressions Improvement (CGI-I) and Severity (CGI-S) subscales (Guy 1976). The CGI-I is a 7-point scale designed to measure symptomatic change at a specific time as compared to baseline. The CGI-I was focused on the core social impairment of autism. Scores range from 1 = ''Very Much Improved'' to 4 = ''Unchanged'' to 7 = ''Very Much Worse.'' The CGI-S is rated on a scale from 1 to 7 (1 = normal, not ill at all; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients). In this report, the CGI-S scores were anchored to degree of social impairment. The primary parent-rated measure used was the aberrant behavior checklist (ABC) (Aman et al. 1985). The ABC is commonly used as a measure of treatment effects in patients with developmental disabilities. This 58-item, informant-based scale is comprised of five subscales. The five subscales are as follows: I. *Irritability* (includes aggression, self-injurious behavior (SIB), irritability, agitation, and crying, 15 items); II. *Lethargy/Social Withdrawal* (includes social

Table 1. Characteristics of Acamprosate Treatment in Six Youth with Autistic Disorder

Age (years)	*Final dose (mg/day)*	*Duration (weeks)*	*Concomitant medications*	*CGI-I score*	*Adverse effects*	*Clinical noted treatment effects*
9	999	10	Aripiprazole	1	None	Improved language understanding, increased verbalizations
12	1,332	28	Clonidine, risperidone	1	Reduced appetite	Increased use of social language, improved eye contact, improved social relatedness
6	999	20	DDAVP, Synthroid	2	Transient mild nausea	Increased social communication, improved eye contact
8	1,332	30	Atomoxetine, guanfacine, risperidone	2	None	Improved social use of language, improved attention, improved eye contact
10	666	14	None	2	None	Improved eye contact, verbalizations, and general social relatedness
11	999	20	Sertraline	4	Reduced appetite	No changes noted

DDAVP = desmopressin; CGI-I = Clinical Global Impressions-Improvement.

withdrawal, 16 items); III. *Stereotypic Behaviors* (7 items); IV. *Hyperactivity* (includes noncompliance, 16 items); and V. *Inappropriate Speech* (4 items). The secondary parent-rated outcome measure used was the social responsiveness scale (SRS) (Constantino et al. 2003). The SRS is a 65-item, parent-completed scale that assesses several aspects of reciprocal social behavior. The SRS gives a total score that is proportional to the level of impairment in reciprocal social behavior. An a priori definition of treatment response was a combined CGI-I score of 1 ''very much improved'' or 2 ''much improved'' and a $\geq 30\%$ improvement on the ABC-Social Withdrawal subscale.

Safety measures

Vital signs, including height, weight, pulse, and blood pressure, were assessed at each clinic visit. A structured assessment of potential side effects using information abstracted from the acamprosate prescribing information was completed at each visit.

Data analysis

All data were recorded in SPSS version 18 for statistical analysis. Potential differences in pre- and post-treatment mean values of all outcome measures employed were calculated using paired *t*-tests. The *t*-tests were for matched samples. Effect sizes were calculated by taking the mean change from baseline to endpoint divided by the standard deviation at baseline.

Results

Characteristics of treatment for each subject are presented in Table 1. Specifics of treatment effect taken directly from clinician notes are also recorded. The mean final dose of acamprosate was 1,110 mg/day ± 172 mg/day (range, 999–1,332 mg/day). The mean duration of treatment was 20 ± 8 weeks (range, 10–30 weeks). The results of the primary and secondary outcome measures are presented in Table 2. The mean CGI-I score at end point was 2.2 (''much improved''). Five subjects met the definition of treatment response. In each case, response occurred by week 8 of treatment and continued up through the last clinical visit (data analyzed from last clinical visit). Acamprosate was well tolerated with no drug discontinuations due to adverse effects noted. Adverse effects experienced by three (50%) subjects were related to gastrointestinal function and included reduced appetite ($n = 2$) and transient mild nausea ($n = 1$).

Discussion

The findings of this initial report on acamprosate use in autism need to be taken in the context of the limitations of the study. These limitations include the small sample size, lack of placebo control, and lack of further subject baseline characterization such as data on cognitive functioning, language ability, and use of standardized instruments to diagnose autistic disorder. Without future use of a control group and blinded evaluation, it will not be possible to determine the true potential impact of acamprosate in autism.

Acamprosate was associated with improvement in social relatedness in this pilot naturalistic open-label trial. Clinical change in social behavior was captured by a mean rating of ''much improved'' on the CGI-I and improvement on both the ABC Social Withdrawal subscale and the total raw score of the SRS. Among parent-report measures, the clinical change noted appeared most

Table 2. Outcome Measure Results

Measure	*Baseline (mean ± SD)*	*End point (mean ± SD)*	p-*value*	*Effect size*[a]
Aberrant Behavior Checklist-Irritability (ABC-I)	15.7 ± 11	12.8 ± 9.9	0.07	–
Aberrant Behavior Checklist- Social Withdrawal (ABC-SW)	16.7 ± 5.0	9.5 ± 4.5	0.002	1.4
Aberrant Behavior Checklist- Stereotypy (ABC-S)	9.0 ± 2.1	6.2 ± 4.2	0.052	–
Aberrant Behavior Checklist- Hyperactivity (ABC-H)	20.2 ± 5.6	11.8 ± 5.6	0.001	1.5
Aberrant Behavior Checklist-Inappropriate Speech (ABC-IS)	1.2 ± 1.9	1.2 ± 1.8	1.0	–
Clinical Global Impressions-Severity (CGI-S)	4.7 ± 0.5	3.8 ± 0.4	0.004	1.8
Social Responsiveness Scale (SRS)	114.7 ± 17.7	101.2 ± 21.1	0.04	0.76

[a]Effect size only computed for corrected *p*-values ≤ 0.05; Computed as mean change from baseline to endpoint divided by SD at baseline.
SD = standard deviation.

sensitive to change on the ABC Social Withdrawal subscale. Hyperactivity as measured by the ABC Hyperactivity subscale also improved.

The next step in studying acamprosate in autism will include a pilot placebo-controlled treatment trial followed potentially by a large-scale controlled trial. Future large-scale study of acamprosate in autism will need to focus on defining the exact clinical impact of the drug across a broader range of symptoms, assessing the tolerability of the drug in a larger sample, and developing potential predictors of treatment response. Given the lack of available effective pharmacologic treatments of core social impairment in autism, further study of acamprosate is clearly warranted.

Disclosures

Dr. Erickson is the inventor on a patent describing use of acamprosate in autism. The patent is held by Indiana University Research and Technology Corporation. Dr. Erickson is on Scientific Advisory Boards and receives research grant support from Seaside Therapeutics, F. Hoffmann-LaRoche, and Novartis. Dr. McDougle is on the Speakers Bureau for and receives research support from Bristol-Myers Squibb Co. Dr. Stigler receives research support from Bristol-Myers Squibb Co. and Forest Pharmaceuticals.

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Address correspondence to:
Craig A. Erickson, M.D.
Department of Psychiatry
Christian Sarkine Autism Treatment Center
Indiana University School of Medicine
James Whitcomb Riley Hospital for Children
702 Barnhill Drive
Room 4300
Indianapolis, IN 46202

E-mail: crericks@iupui.edu