

## Brief Report: Case Reports on Naltrexone Use in Children with Autism: Controlled Observations Regarding Benefits and Practical Issues of Medication Management

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### INTRODUCTION

Autism is a developmental disorder characterized by pervasive impairments in social interaction and communication, as well as restricted range of activities and interests. The prevalence of this neurobiologic disorder is currently estimated at 1 : 1000 (National Institutes of Health, 1995). Although the specific etiology for autism is unknown, it has been associated with other medical or genetic conditions in approximately 10% of cases (Bailey, Phillips, & Rutter, 1996; Rutter, Bailey, Button, & Le Couteur, 1994). Research emphasis has been on genetic, immunologic, metabolic, and neurochemical factors which may play a role in creating this spectrum disorder. Regardless of the etiology, autism has a tremendous impact on children and their families. Primary intervention for autism is currently educational and behavioral. However, medication may play an important role in the facilitation of learning and appropriate behavior.

Naltrexone is a long-acting opioid antagonist proposed as an effective treatment for autism based on the theory of a dysfunctional endogenous opioid system in this disorder. Panksepp (1979) proposed that autism results from a failure of striatal beta endorphins to diminish with maturation. More recently, Chamberlain and Herman (1990) hypothesized a complex model involving dysfunction in brain melatonin, opioid precursors, and monoamines in autism. Limited objective support for endorphin dysfunction in autism has been evidenced by plasma and cerebrospinal fluid studies

measuring beta endorphins in children with autism; these studies are summarized in an article by Gillberg (1995).

Although the efficacy of naltrexone in the treatment of autism remains somewhat controversial, a majority of studies have indicated some beneficial effects of naltrexone in individuals with autism. Barrett, Feinstein, and Hole (1989), using a single-subject experimental design under double-blind, placebo-controlled conditions, showed a decrease in self-injurious behavior to near-zero rates for naltrexone versus naloxone. Campbell *et al.* (1993) studied 41 children and found significant reduction in hyperactivity but no effect on discrimination learning. Bouvard *et al.* (1995), in a double-blind study of 10 children with autism, demonstrated modest behavioral improvements which appeared to correlate with normalization of elevated plasma chemistries. Kolmen, Feldman, Harden, and Janosky (1997) reported the results of a double-blind, placebo-controlled crossover study and concluded that naltrexone was associated with modest improvement in behavior but no change in learning for 11 of the total 24 children studied. Willemson-Swinkels, Buitelaar, and Van Engeland (1996) completed a double-blind, placebo-controlled study of 23 children with autism in which teacher reports indicated a decrease in hyperactivity and irritability but no effect on social and stereotyped behaviors. A recent follow-up study by Willemson-Swinkels *et al.* (1999) indicated continued modest improvement in hyperactivity for 6 children who showed initial response to naltrexone and were monitored during a 6-month continuation treatment. Thus, previous studies have indicated that naltrexone has benefit in decreasing self-injurious behavior and hyperactivity. Indeed, Campbell (1996) has proposed that children with autism should be considered for a

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trial of naltrexone given its benefits and safety profile, although this proposal was debated in the same journal (Harris, 1996).

Clinical use of naltrexone has been less extensive than might be expected given this endorsement. One of the reasons for this in our clinical practice seems to be difficulty in administration of this extremely bitter-tasting medication. Another reason may be an impression of less than dramatic behavioral changes despite the initial hope for improved social interaction with use of this medication in autistic populations. The purpose of this study was to obtain controlled observations of subjects in our clinical practice. These observations included not only traditional parent, teacher, and clinical ratings, but also videotaped observations of behavior in home and school settings. Videotaped observations were used in order to assess the effects of naltrexone on social behaviors in "natural" settings. We hypothesized that social gains might be more readily apparent within the child's typical environment rather than a clinical setting and decided to use social initiations on videotaped samples as one of our primary measures of medication response. A double-blind, placebo-controlled case report format was chosen to provide more objective measures of behavioral changes.

## METHOD

Eight boys between the ages of 2 years 10 months and 9 years 2 months participated; mean age was 4 years, 4 months. All had comprehensive tertiary evaluations through our facility and met criteria for autism based on DSM-IV criteria and the Autism Diagnostic Interview-Revised (American Psychiatric Association, 1994; Lord *et al.*, 1994). All of the children presented with behaviors typical of young children with autism including attention difficulties, poor social relatedness, and impaired communication skills. The Child Evaluation Center is a university-affiliated facility which provides multidisciplinary evaluations for children with a variety of developmental disabilities. Parents were offered the opportunity to participate in the study at the time of initial diagnosis or at follow-up visits. They were informed of the nature of the study and provided with an extensive informed consent outlining benefits and potential side effects of naltrexone. Placebo was an acetaminophen tablet with bitter flavoring as formulated by the Kosair Children's Hospital pharmacy. Naltrexone dose was 1.5 mg/kg every other day. Patients were randomly assigned by the pharmacy to initial treatment of either naltrexone or placebo. None of the participants knew

which medication was being administered. Parents were provided with information about strategies for administering the medication in order to increase compliance.

Phase I of the study lasted 4 weeks and was followed by a 1-week washout after which time the children received the alternate treatment. A 4-week period was chosen to allow time for drug effect. Behavioral measures and videotaping of the child were obtained 1 week prior to Phase I (baseline), at the conclusion of Phase I (last week of treatment) and at the conclusion of Phase II (last week of the alternate treatment).

Parents were interviewed following Phase I and II to obtain information regarding potential side effects and compliance. Clinician ratings were based on informal observation at clinic visits and included global measures using Likert-type scales ranging from 1 (*very much improved*) to 7 (*very much worse*). The clinician completing the rating scales is a developmental pediatrician at the Child Evaluation Center with 6 years of experience. She also filled out the Childhood Autism Rating Scale on three occasions for each child (Schopler, Reichler, & Renner, 1988). Parents completed ratings of global improvement using a Likert-type scale at baseline, Phase I and Phase II. In addition, parents filled out behavior checklists and Parenting Stress Index-Distractibility Scales or the Child Behavior Checklist-Attention Problems Scale to assess possible side effects and attention (Abidin, 1995; Achenbach, 1991).

The Social Interaction and Stereotyped Behavior Scales of the Gilliam Autism Rating Scales (GARS) was also completed by parents to assess changes in social and behavioral areas (Gilliam, 1995). The GARS is a checklist consisting of four subtests (stereotyped behaviors, communication, social interaction, and development in first 3 years of life) which is designed to be used by parents and/or professionals in identifying and estimating the severity of autism for individuals age 3 to 22 years. In addition, videotaped observations of the child's behavior were obtained for 20 minutes at home and 20 minutes in a school-type setting. The 20-minute period included 10 minutes of structured activity and 10 minutes of unstructured play. Structured activities included mealtime at home and planned group times at school. Unstructured time was free play either with family members or peers and adults at school.

Two raters counted social behaviors occurring during the 40 minutes of videotaped activity for child. The raters were both psychologists at the Child Evaluation Center, each with at least 10 years of clinical experience. Given the base rate of various social behaviors occurring during the taping, it was decided that only one category of social behavior could be meaningfully

and reliably compared across subjects for each drug phase due to the overall low rate of social behaviors displayed by subjects. Targeted social initiations were defined as directing eye gaze toward another person or physically contacting a person in a nonaggressive social manner. Frequency of initiations was counted. Instances of eye gaze or physical contact controlled by adults were not counted. Responses to the voice or physical activity of an adult with a social eye gaze were counted as social initiations. Interrater reliability was established by having raters review videotapes of children not in the study until agreement was greater than 95% on identifying social behaviors.

Responders were defined a priori as those who demonstrated an increased frequency of social interaction in home and school videotaped observations during the naltrexone trial as compared to the placebo trial. Rating scales completed by parents and clinicians were correlated with home and school behaviors to determine which instruments corresponded to observed changes in social behavior in the child. Rating scale scores were positive (+) if the subject displayed improvement on that measure for naltrexone as compared to placebo; negative (–) if the child had no scaled score difference between placebo and naltrexone or if the child had worsening behavior. A phi coefficient was used to test agreement of clinical rating scale scores with the responder/nonresponder classification.

## RESULTS

Of the original eight children enrolled in the study, two (25%) withdrew due to problems with compliance with the medication protocol. Parents of these children reported problems in administering the naltrexone or the placebo, and suggestions made by the researchers regarding strategies for administration were ineffective. Both boys dropped out within the first 4 weeks of the study. Parents of three children (37.5%) reported no problems in giving medication or placebo, and no special procedures were needed for administration. The other three boys (37.5%) took the medication if crushed up and mixed in syrup or orange juice. None of the six subjects who completed the study reported any side effects.

Table I displays the results of behavioral measures and videotaped observations for subjects during placebo and naltrexone trials. Four of six children showed an increased number of social initiations on naltrexone as compared to placebo. Five of six children showed improved scores on the GARS stereotypies

**Table I.** Behavioral Measures for Children on Placebo and Naltrexone Trials

	Subject					
	1	2	3	4	5	6
Social initiations <sup>a</sup>						
Placebo	16	8	15	9	16	12
Naltrexone	4	16	18	8	22	26
Clinician rating <sup>b</sup>						
Placebo	4	3	4	3	4	4
Naltrexone	4	4	2	3	4	2
Parent rating <sup>b</sup>						
Placebo	3	3	5	4	3	4
Naltrexone	2	6	1	4	4	2
Attention problems <sup>c</sup>						
Placebo	80	54	85	53	70	90
Naltrexone	35	50	66	60	84	75
CARS-Total <sup>d</sup>						
Placebo	45	49	45	45	48	50
Naltrexone	43	41	45	46	49	33
GARS-Social <sup>e</sup>						
Placebo	17	16	29	11	28	20
Naltrexone	20	12	18	23	25	17
GARS-Stereo <sup>e</sup>						
Placebo	22	23	29	12	27	25
Naltrexone	23	21	16	7	14	15

<sup>a</sup> Number of social initiations defined as looking at person during 40-minute observation period.

<sup>b</sup> Clinician and parent rating of global improvement from 1 (*very much improved*) to 7 (*very much worse*).

<sup>c</sup> *T* score for Parenting Stress Index—Distractibility or Child Behavior Checklist—Attention Problems. Higher scores reflect greater attention problems.

<sup>d</sup> Childhood Autism Rating Scale. Higher total score indicates more autistic behaviors.

<sup>e</sup> Gilliam Autism Rating Scale raw scores for Social Interaction and Stereotyped Behavior subscales. Higher scores indicate increased impairment in each area.

scale for naltrexone as compared to placebo. Four out of six children showed improvement in attention problems and social scale of the GARS. No pattern was noted on the global parent and clinician rating scales.

Table II delineates subject response on behavior measures as compared to response on videotaped observations. A plus sign denotes improvement in naltrexone versus placebo for each behavioral measure; a minus sign denotes no change or worsening of behavior. Agreement of each clinical measure with categorization of responders according to videotaped social initiations was then calculated with phi coefficient. The Social Scale of the GARS was the only behavior measure to correlate with response on videotaped observation. Global clinician and parent ratings and other behavioral measures showed no more than chance levels

**Table II.** Agreement of Clinical Measures in Identifying Medication Response<sup>a</sup>

Subject	Medication response <sup>b</sup>	Clinician rating	Parent rating	PSI/CBC attention	CARS total	GARS Social	GARS Stereo
1	–	–	+	+	+	–	–
2	+	–	–	+	+	+	+
3	+	+	+	+	–	+	+
4	–	–	–	–	–	–	+
5	+	–	–	–	–	+	+
6	+	+	+	+	+	+	+
Phi coefficient		.50	.00	.25	.00	1.0	.63
<i>p</i> value		.22	1.0	.54	1.0	.01	.12

<sup>a</sup> Improvement is indicated by plus sign; no change or worsening behavior is indicated by a minus sign. Phi coefficients indicate the agreement of each measure (i.e., improved or not improved) with medication response or nonresponse for each subject.

<sup>b</sup> Number of social initiations—videotaped observations.

of agreement with response status as defined by social initiations on videotaped behavioral observation.

## DISCUSSION

Inspection of clinical study results indicate relative improvement on several measures for naltrexone versus placebo: (a) social initiations on videotaped samples (4 out of 6 with improved scores); (b) social scale of the GARS (4 out of 6 with improved scores); (c) stereotypies scale of GARS (5 out of 6 with improved scores); and (d) attention problems (4 out of 6 improved). Differences in individual scores on behavioral measures were not large and statistical significance was not calculated due to small number of subjects. It might very well be that these differences could simply be attributed to chance variance. No differences were detected in global parent and clinician ratings. This is notable given the fact that previous studies have indicated improvement in activity level and behavior (Campbell *et al.*, 1993; Kolmen *et al.*, 1997; Willemson-Swinkels *et al.*, 1996). Possible explanations for the lack of evidence of change in these areas include the fact that the CARS and other global rating scales are not specific enough to target these individual behaviors and/or that any improvements were too modest to be detected.

Despite the small number of cases, the subjects are representative of the population seen in our clinical practice. Six of the participants were children who had recently been diagnosed with autism and whose parents hoped that medication would facilitate learning. The other two were older children who had been followed through the Center for several years; one of these boys had been tried on several previous medications due to concerns about activity level and impulse con-

trol. Parents were routinely invited to participate in the study upon initial diagnosis or reevaluation. A 4-week trial was chosen because this is after the amount of time in which parents and clinicians expect to see behavioral changes.

In this study, we had particular interest in looking at changes in social interaction. Naltrexone was initially proposed as a medication with benefits in the area of social interaction, although very few studies have supported this (Borghese *et al.*, 1991; Herman, Hammock, & Arthur-Smith, 1986). We felt that videotaped observations of the child in more natural settings might better detect changes in social interaction. Our subjects generally demonstrated few initiations of social behaviors and most of the measured behaviors fell under the category of “low level” initiations including imitation, echolalia, observations of others’ actions, and movement into the proximity of others. The paucity and primitive nature of early social behaviors in children with autism may make it more difficult to measure changes in social interaction, particularly in a clinical setting. Even small gains in the social area may be important in this population and have implications for further behavioral intervention. It is encouraging that four out of six boys showed increases in number of social initiations of videotaped samples, although in only two of the four were changes dramatic. Certainly, additional controlled studies of naltrexone’s impact in social behaviors are warranted, perhaps utilizing extensive videotaping in typical situations for the child.

However, from a practical standpoint, it is not going to be feasible to measure changes in social behavior based on videotaped observations. It is too costly and time consuming to obtain and analyze videotaped samples. It is of interest from a clinical perspective that the GARS social scale correctly identified all responders

based on videorecorded social initiations. Although larger numbers of subjects are needed to validate this relationship, the GARS social scale may prove a helpful measure of social interaction in the practitioner's office.

Another clinical issue raised by this study is the difficulty with medication compliance, particularly with a bitter-tasting medication such as naltrexone. Two out of eight children discontinued participation in the study because they could not take the medication. Medication taste and texture become particular issues in children with autism, many of whom have extreme food preferences and very limited food repertoires. We have tried a variety of techniques for disguising medication including crushing the medication in chocolate syrup, cherry syrup, and juice, placing the medication in a favorite food, or crushing the tablets and placing it in a capsule for older children. However, many parents express concern that if the medication is placed in a favorite food or beverage, it may dissuade the child from eating the few foods he currently likes. Difficulties with medication compliance may necessitate coordinated efforts between the prescribing physician and behavioral specialists in autism. Parents in this study reported no significant side effects in accordance with other studies that have indicated a good short-term safety and side effect profile for this medication. However, the medication's taste serves as a major deterrent for an extended trial, both for this study and in day-to-day clinical practice. Such factors cannot be overlooked in choosing and establishing a medication regimen.

In summary, our case studies point to some of the issues that may have contributed to an ambiguous attitude toward naltrexone use in children with autism. As previously reviewed, naltrexone is a medication that has documented benefits in several well-controlled studies, although most studies characterize these benefits as "modest." In recent years, parents of children with autism have increasingly expressed interest in trying medications or alternative therapies which may aid with behavior and development. Medication choices, while increasing, are still quite limited. Naltrexone appears to be a reasonable choice given its safety profile and previous studies showing efficacy.

Our experience indicates possible mild improvement in social interaction as measured by videotaped observations in which social initiations were counted. Those who showed increased social initiations on videotaped observations also showed improvement on the social scales of the GARS, but changes in individual scores were often minimal. In fact, many of the behavioral changes were so modest as to be difficult to

detect on standard measures raising the question of clinical significance and what the most appropriate measures of target behaviors should be. Problems with medication compliance resulted in one fourth of patients dropping out of the study and constitute a major obstacle for continued use in many patients. These issues may preclude the use of naltrexone as an initial treatment choice for behavioral difficulties in children with autism and deserve the careful consideration of the practitioner.

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