LACK OF BENEFIT OF A SINGLE DOSE OF SYNTHETIC HUMAN SECRETIN IN THE TREATMENT OF AUTISM AND PERVASIVE DEVELOPMENTAL DISORDER

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ABSTRACT

Background   Secretin is a peptide hormone that stimulates pancreatic secretion. After recent publicity about a child with autism whose condition markedly improved after a single dose of secretin, thousands of children with autistic disorders may have received secretin injections.

Methods   We conducted a double-blind, placebo-controlled trial of a single intravenous dose of synthetic human secretin in 60 children (age, 3 to 14 years) with autism or pervasive developmental disorder. The children were randomly assigned to treatment with an intravenous infusion of synthetic human secretin (0.4 µg per kilogram of body weight) or saline placebo. We used standardized behavioral measures of the primary and secondary features of autism, including the Autism Behavior Checklist, to assess the degree of impairment at base line and over the course of a four-week period after treatment.

Results   Of the 60 children, 4 could not be evaluated — 2 received secretin outside the study, and 2 did not return for follow-up. Thus, 56 children (28 in each group) completed the study. As compared with placebo, secretin treatment was not associated with significant improvements in any of the outcome measures. Among the children in the secretin group, the mean total score on the Autism Behavior Checklist at base line was 59.0 (range of possible values, 0 to 158, with a larger value corresponding to greater impairment), and among those in the placebo group it was 63.2. The mean decreases in scores over the four-week period were 8.9 in the secretin group and 17.8 in the placebo group (mean difference, −8.9; 95 percent confidence interval, −19.4 to 1.6; $P=0.11$). None of the children had treatment-limiting adverse effects. After they were told the results, 69 percent of the parents of the children in this study said they remained interested in secretin as a treatment for their children.

Conclusions   A single dose of synthetic human secretin is not an effective treatment for autism or pervasive developmental disorder. (N Engl J Med 1999; 341:1801-6.)
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A UTISM is a developmental disorder characterized by qualitative abnormalities of social interaction, impairments in communication, and unusual forms of repetitive behavior.[1] Research on drug treatment has been directed toward the management of symptoms. Serotonergic mechanisms have been implicated in some of the symptoms of autism,[2] and the results of recent clinical trials indicate that serotonergic drugs can lessen the severity of symptoms associated with autism and related conditions.[3-5]

In the absence of proven drug treatment for the core symptoms of autism, unproven treatments are widely used.[6] Some of these treatments are based on theories of abnormal intestinal permeability, according to which excessive absorption of peptides derived from the gut may affect central serotonergic, opioid, and perhaps other neurotransmitter systems.[7] Indeed, there are many parents who report that their children with autism have a variety of gastrointestinal symptoms (e.g., chronic diarrhea).

Recently, a three-year-old child with autism and chronic diarrhea underwent an endoscopic procedure that included the intravenous administration of secretin to assess pancreatic exocrine function. Within a week after the procedure, the child's parents noticed dramatic improvements in his behavior and language skills.[8] Media attention focusing on anecdotal reports of secretin-related effects in children with autism has escalated into reports that secretin may represent a "cure" for autism. There are reports of the sale of sham secretin, price gouging, and other forms of profiteering.[9] It is estimated that at least 2500 children with autism have received secretin injections.[10] We are aware, however, of the published results of only one open-label study, in which it was used in three boys with autism.[11]

Secretin is a peptide hormone composed of 27 amino acids, which is released from S cells of the duodenum in response to the presence of acidic contents in the stomach. Secretin increases the volume and bicarbonate content of secretions from pancreatic acinar cells.[12] Secretin is derived from the duodenum of pigs, and purified porcine secretin (Ferring Laboratories, Suffern, N.Y.) was approved by the Food and Drug Administration in 1981 for single-dose use in the diagnosis of gastrointestinal disorders. No data are available on the safety of repeated

doses over time, and there are no data regarding its safety and efficacy in children.

Pure human secretin was synthesized and manufactured in 1998 by ChiRhoClin (Silver Spring, Md.). The human and porcine forms of secretin have equivalent kinetics and pharmacologic effects on the exocrine pancreas in humans.[13] We conducted a randomized, double-blind, placebo-controlled trial of synthetic human secretin in children with autistic disorders.

METHODS

Subjects

We identified 60 children from a sample of 94 children who were referred by the Treatment and Evaluation of Autism and Communication Handicaps program of the Department of Psychiatry at the University of North Carolina or whose parents responded to notices about this study placed in the newsletter of an autism-support group. The inclusion criteria for the study were a previous diagnosis of autism; an age between 3 and 14 years; no previous secretin treatment; no diagnosis of pancreatitis, inflammatory bowel disease, or gastrinoma; and written, voluntary informed consent for participation by a parent or legal guardian.

Children who met all inclusion criteria were screened for autism. The diagnosis of autism was made according to the criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV),[14] the Childhood Autism Rating Scale,[15] and the Autism Behavior Checklist.[16] A diagnosis of autism was given to children who met the criteria for autism of the DSM-IV on the basis of observation of the child and a structured diagnostic interview of a parent, who had a score on the Childhood Autism Rating Scale of 30 or more (range of possible scores, 0 to 60), and who had a score on the Autism Behavior Checklist of 60 or more (range of possible scores, 0 to 158). For both scores, a larger value corresponds to more severe impairment. A diagnosis of pervasive developmental disorder, not otherwise specified, was given to children who had severe impairments in either socialization or communication, or who engaged in repetitive behavior, as documented by observation and the diagnostic interview, but who did not meet the DSM-IV criteria for autism. This evaluation represented consensus ratings from the study clinician (on the basis of observation and the DSM-IV diagnostic interview), the referring clinician (on the basis of the Childhood Autism Rating Scale), and the parent (on the basis of the Autism Behavior Checklist).

Of the 60 children who entered the study, 40 met the criteria for autism (mean score on the Childhood Autism Rating Scale, 38.3; mean score on the Autism Behavior Checklist, 74.6), and 20 met the criteria for pervasive developmental disorder, not otherwise specified (mean score on the Childhood Autism Rating Scale, 27.9; mean score on the Autism Behavior Checklist, 41.2). A comparison of the two diagnostic subgroups revealed significantly higher scores on the Childhood Autism Rating Scale (P<0.001) and the Autism Behavior Checklist (P=0.05) in the subgroup with autism than in the subgroup with pervasive developmental disorder.

None of the children had serious medical problems according to the history and medical examination. The human subjects committee of the Olson Huff Center for Child Development approved the study protocol.

Treatment

After a two-week base-line period, the 60 children were randomly assigned to receive either a single infusion of secretin or a single infusion of a saline placebo. A stratified randomization scheme based on a "median split" of the final subject sample according to the median age (eight years) was used.

The vials of synthetic human secretin contained a sterile, lyophilized powder consisting of 16 μg of synthetic human secretin,

1.5 mg of cysteine hydrochloride, and 20 mg of mannitol. The secretin was reconstituted with 8 ml of normal saline per vial. The children were weighed, and a single dose of 0.4 μg per kilogram of body weight was prepared (a volume of 0.2 ml per kilogram). For the children in the placebo group, an identical-appearing syringe containing 0.2 ml of normal saline per kilogram was prepared. The doses were administered by slow intravenous injection over a period of one minute. Secretin and placebo were administered with the use of a double-blind procedure.

Outcome Measures

Detailed assessments of each child's behavioral symptoms were conducted by the study clinicians, by the child's parents, and by the child's school or preschool teacher. Behavioral assessments were conducted at the end of each of the two base-line weeks, on the first and second days after infusion, and at the end of the first, second, and fourth weeks after infusion.

Communication skills were measured with the communication subscale of the Vineland Adaptive Behavior Scales.[17] On this subscale, the standard score has a mean of 100 and a standard deviation of 15, and the range of possible scores is less than 20 to greater than 160, where higher scores mean less impairment. The subscale is a 63-item structured clinical interview that measures age-appropriate communication skills and provides a standardized score for communication ability. Separate assessments were conducted of both the parent's perception of the child's behavior in the home and the teacher's perception of the child's behavior in school.

The severity of autistic symptoms was measured with the Autism Behavior Checklist,[16] a 57-item standardized clinical-rating scale that provides an overall score for severity (total score, 0 to 158, with higher values corresponding to greater impairment) and five subscores (relating to sensory function, social relatedness, body and object use, language, and socialization). The Clinical Global Impression Scale[18] was used to measure eight separate features associated with autism (response to social interaction, social initiation, use of speech, types of repetitive behavior, behavior problems, activity level, sleep problems, and digestive problems) on a standardized, seven-point Likert scale, with 7 indicating "very much worse," 4 "no change," and 1 "very much improved."

Adverse effects of treatment were measured with the Treatment Emergent Symptoms Scale,[19] a standardized rating scale that measures the occurrence or nonoccurrence of 24 potential side effects of medication in six categories (gastrointestinal, urinary, respiratory, skin, neurologic, and psychological). Each side effect is indexed in terms of observable behavior and is scored on a three-point Likert scale, with 2 denoting severe, 1 mild, and 0 absent. The Vineland Adaptive Behavior Scales and Treatment Emergent Symptoms Scale were completed by study clinicians, and the Clinical Global Impression Scale and Autism Behavior Checklist were completed by the child's parents. All persons who performed the behavioral assessments were unaware of each child's treatment status.

Statistical Analysis

For each outcome measure, two-by-six analysis of variance with repeated measures was used to assess the effects of the treatment group (secretin or placebo), the time of assessment (at base line and day 1, day 2, week 1, week 2, or week 4 after infusion), and the interaction between treatment group and time of assessment.[20] For each outcome measure, the changes from base-line scores were computed for all assessment periods after treatment, and the resulting changes in scores were analyzed with the use of t-tests and estimates of 95 percent confidence intervals.[20] Chi-square tests with Yates' correction[20] were used to compare the rates of response in treatment groups and to determine whether response was related to diagnostic variables (autism vs. pervasive developmental disorder), demographic variables (sex and age), or clinical variables (use of adjunctive medication). To examine the response to treatment at the level of the individual subject, a criterion for clinically significant positive response was established before analysis. Significant positive response was defined as a score on the Clinical Global

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 60 SUBJECTS.*

VARIABLE	SECRETIN	PLACEBO
No. of children	30	30
Age (yr)	7.6±3.0	7.4±2.0
IQ score	65.6±23.2	60.1±25.2
Diagnosis (%)		
Autism	64	70
Pervasive developmental disorder	36	30
ABC total score	62.7±22.2	66.2±23.4
CARS total score	34.4±3.8	37.0±5.9
Seizures (%)	20	17
Medication (%)†	27	37
No. of behavioral problems‡	3.1±2.7	3.1±1.4
No. of repetitive types of behavior‡	4.2±1.6	3.4±1.4
No. of sleep problems‡	0.9±0.9	1.3±0.8
No. of digestive problems‡	1.2±1.4	1.8±1.6

*Plus–minus values are means ±SD. ABC denotes Autism Behavior Checklist, and CARS Childhood Autism Rating Scale.

†This variable refers to psychotropic drugs (including stimulants, antidepressants, anxiolytic drugs, and antipsychotic drugs).

‡Values are derived from a standard list of possible behavioral problems (maximum, seven), types of repetitive behavior (maximum, nine), sleep problems (maximum, three), or digestive problems (maximum, six).

	Base Line	Day 1	Day 2	Week 1	Week 2	Week 4
NO. OF CHILDREN						
Secretin	28	27	27	27	26	25
Placebo	28	26	26	25	25	24

Figure 1. Mean Score on the Social Interaction Subscale of the Clinical Global Impression Scale at Each Assessment.

The initial sample for each group was 30 children. The numbers of children at each evaluation reflect reduced samples due to withdrawal and loss to follow-up (two children in each group) and to the fact that data were missing for some children at each evaluation.

Impression Scale of either 2 (much improved) or 1 (very much improved) for any of the eight features assessed at two or more of the five follow-up evaluations (day 1, day 2, week 1, week 2, or week 4). P values for all statistical tests were two-tailed. All data were collected before the codes for treatment group were broken.

RESULTS

Subjects

Fifty-six of the 60 children completed the study (28 per group). Four children discontinued the study after the administration of the infusion. Two children (both assigned to secretin treatment) were withdrawn because of their parents' wish that their children begin receiving secretin treatment outside the study protocol, and the families of two children (both assigned to placebo treatment) could not be reached for collection of follow-up data.

The clinical and demographic characteristics of the two treatment groups are shown in Table 1. There were no significant differences between the treatment groups with respect to any of the clinical or demographic variables measured at base line.

Comparisons of Treatment Groups

Each of the outcome measures was examined for changes in the severity of symptoms that were related to treatment (placebo or secretin), time of assessment (base line, day 1, day 2, week 1, week 2, or week 4), or the interaction of these factors. Two patterns of results were found. First, secretin was not associated with significantly greater improvements on any of the 16 outcome measures than was placebo
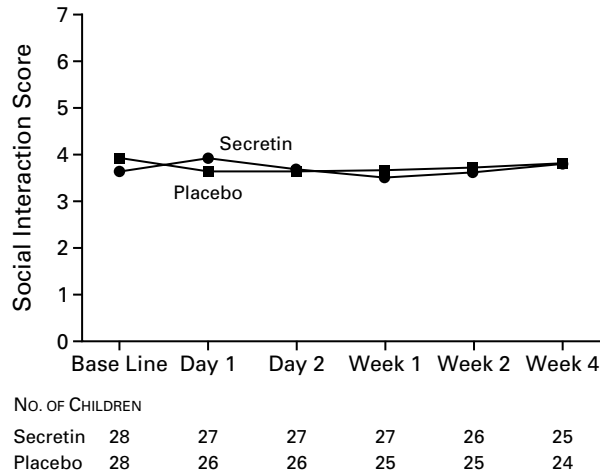
(P values ranged between 0.20 and 0.88). Scores were not significantly better with secretin treatment than with placebo for the overall severity of autistic symptoms (P=0.33), communication skills (P=0.21), specific diagnostic features of autism (P=0.73), or nonspecific features of autism (P=0.88). An example of this pattern is shown in Figure 1.

Second, significant decreases from base line in the severity of symptoms on 6 of the 16 outcome measures were reported for both the placebo and the secretin groups over the course of the assessment period (Autism Behavior Checklist total score, P<0.001; Autism Behavior Checklist sensory-function score, P<0.001; Autism Behavior Checklist social-relatedness score, P<0.001; Autism Behavior Checklist language score, P=0.05; Autism Behavior Checklist socialization score, P<0.001; and Clinical Global Impression Scale speech score, P=0.02), but there were no differences between treatment groups in the magnitude of these decreases over time. An example of this pattern is shown in Figure 2. The results of subgroup analyses of the outcome measures among the children with autism and among those with pervasive developmental disorder, not otherwise specified, showed a similar pattern for each subgroup.

Anecdotal reports of the effects of secretin have been mixed with regard to the timing of the reported improvement of symptoms. For this reason, we examined the change from base-line scores in each treatment group both one week and four weeks after infusion for all of the outcome measures. For all 14 outcome measures at one week (Table 2) and all 16
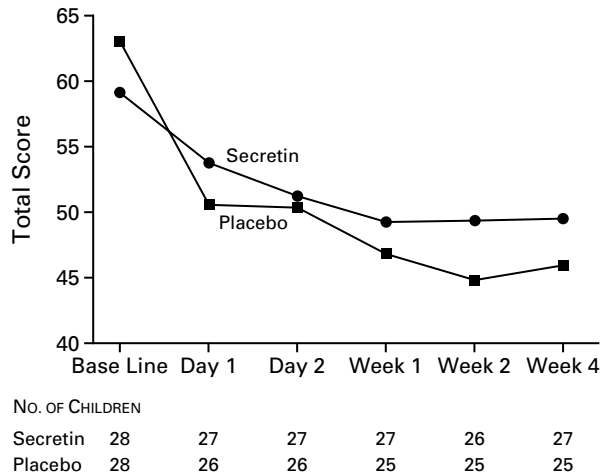
Figure 2. Mean Total Score on the Autism Behavior Checklist at Each Assessment.

The initial sample for each group was 30 children. The numbers of children at each evaluation reflect reduced samples due to withdrawal and loss to follow-up (two children in each group) and the fact that data were missing for some children at each evaluation.

outcome measures at four weeks (Table 3), comparisons of the change from base-line scores showed no significant differences between the secretin and placebo groups. Similar results were obtained when the subgroup with autism and that with pervasive developmental disorder were analyzed separately.

Response of Individual Subjects

Nine of the 27 children in the secretin group for whom there were complete data (33 percent) and 7 of the 25 children in the placebo group for whom there were complete data (28 percent) were considered to have had a response to treatment. There was no significant difference between the treatment groups in the proportions of children who met the criteria for a positive response (P=0.68). Within the secretin group there were no significant associations between response status and diagnosis, age, IQ, presence or absence of digestive symptoms, or use or nonuse of adjunctive medication (P>0.35 for all comparisons).

Adverse Events

None of the children had treatment-limiting side effects. Comparisons of the secretin and the placebo groups showed marginally higher severity scores on the Treatment Emergent Symptoms Scale for the children in the secretin group than for those in the placebo group with respect to decreased activity level (P=0.15).

Parent Interviews

Parents of all of the children who completed the study were interviewed at its conclusion to deter-mine their intentions with respect to future treatments for their children. Before the interview, the parents of each child were made aware of their child's treatment assignment, the specific study outcomes of their child, and the overall results of the study with the use of a standardized script. Sixty-nine percent of the parents remained interested in secretin as a form of treatment for their children (63 percent of the parents of children in the secretin group and 76 percent of the parents of children in the placebo group).

DISCUSSION

We used a set of standard outcome measures to compare children with autism or pervasive developmental disorder who received either a single dose of synthetic human secretin or placebo under double-blind conditions. We found no significant effects of secretin treatment. This lack of effect was seen overall, for the subgroup with autism, and for individual children. Furthermore, decreases in the severity of symptoms with respect to some of the outcome variables were reported over time for both treatment groups. The 95 percent confidence intervals for the differences from base-line scores provide estimates of the plausible changes in the severity of symptoms that could be obtained with the measures we used. The 95 percent confidence intervals for the differences between the groups were narrow, indicating that the differences provide a reasonable estimate of the plausible effects of secretin treatment. Furthermore, the bounds of the 95 percent confidence intervals indicated that secretin-related improvements in the severity of symptoms amounted to a change of no more than 15 percent from base-line levels for any of the measures we used. This finding suggests that although we could not rule out small improvements related to secretin treatment, improvements of this magnitude would not be clinically meaningful for children with autism or related disorders.

Our study had several weaknesses. First, this was a short-term study, and it is unlikely that significant changes in behavior can occur in a brain-based disorder within days or weeks. Second, this was a single-dose study, and multiple doses may prove to be more efficacious. We conducted a short-term evaluation of a single dose of secretin to provide a replication of the circumstances of the anecdotal reports of improvement observed after secretin treatment.[8-11] Third, recent studies have used other diagnostic schedules to identify autistic disorders,[21] and specific subtypes of autism quantified according to these schedules may differ in the potential for response to treatment with secretin. Finally, we used synthetic secretin even though the majority of anecdotal reports of the effects of secretin have been based on the use of the biologic (porcine) product. Given that synthetic human secretin and porcine secretin have equivalent pharmacologic effects in humans[13] and that porcine

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TABLE 2. CHANGE FROM BASE LINE IN MEASURES OF AUTISTIC BEHAVIOR AND ASSOCIATED FEATURES OF AUTISM
ONE WEEK AFTER INFUSION.*

MEASURE	SECRETIN		PLACEBO		DIFFERENCE BETWEEN GROUPS	
	NO. OF CHILDREN†	MEAN CHANGE (95% CI)	NO. OF CHILDREN†	MEAN CHANGE (95% CI)	MEAN DIFFERENCE (95% CI)	P VALUE
Autism Behavior Checklist						
Sensory function	27	1.5 (0.4 to 2.6)	25	2.8 (0.8 to 4.8)	−1.3 (−3.5 to 1.0)	0.24
Social relatedness	27	2.6 (−0.3 to 5.4)	25	5.5 (1.3 to 9.7)	−3.0 (−7.7 to 1.8)	0.23
Body and object use	27	2.4 (0.2 to 4.6)	25	3.6 (0.1 to 7.0)	−1.2 (−5.6 to 2.1)	0.54
Language	27	1.1 (−0.8 to 3.0)	25	2.6 (0.4 to 4.7)	−1.5 (−4.1 to 1.2)	0.29
Socialization	27	1.8 (0.4 to 3.3)	25	1.8 (0.04 to 3.5)	0.02 (−2.1 to 2.1)	0.98
Total score	27	9.4 (2.6 to 16.2)	25	16.2 (7.8 to 24.6)	−6.8 (−16.6 to 3.1)	0.19
Clinical Global Impression Scale						
Response to social interaction	27	0.1 (−0.4 to 0.7)	25	0.1 (−0.4 to 0.6)	0.1 (−0.6 to 0.8)	0.85
Social initiation	27	0.3 (−0.1 to 0.7)	25	0.4 (−0.1 to 0.8)	−0.03 (−0.4 to 0.3)	0.92
Use of speech	27	0.2 (−0.2 to 0.6)	25	0.4 (−0.02 to 0.8)	−0.2 (−0.7 to 0.3)	0.50
Types of repetitive behavior	27	0.1 (−0.3 to 0.5)	25	0.3 (−0.2 to 0.8)	−0.2 (−0.8 to 0.4)	0.50
Behavior problems	27	0.4 (0.0 to 0.8)	25	0.0 (−0.4 to 0.4)	0.4 (−0.1 to 0.9)	0.10
Activity level	27	0.1 (−0.3 to 0.4)	25	−0.2 (−0.6 to 0.2)	0.3 (−0.2 to 0.8)	0.31
Sleep problems	25	−0.1 (−0.6 to 0.5)	24	−0.3 (−0.8 to 0.2)	0.2 (−0.4 to 0.9)	0.55
Digestive problems	26	−0.2 (−0.8 to 0.4)	24	0.04 (−0.4 to 0.5)	−0.2 (−0.9 to 0.4)	0.50

*CI denotes confidence interval.

†The initial sample size for each group was 30. The numbers of children listed reflect reductions due to withdrawal and loss to follow-up (two children in each group) and the fact that data were missing for some children at each evaluation.

TABLE 3. CHANGE FROM BASE LINE IN MEASURES OF AUTISTIC BEHAVIOR, COMMUNICATION SKILLS, AND ASSOCIATED FEATURES
OF AUTISM FOUR WEEKS AFTER INFUSION.*

MEASURE	SECRETIN		PLACEBO		DIFFERENCE BETWEEN GROUPS	
	NO. OF CHILDREN†	MEAN CHANGE (95% CI)	NO. OF CHILDREN†	MEAN CHANGE (95% CI)	MEAN DIFFERENCE (95% CI)	P VALUE
Autism Behavior Checklist						
Sensory function	27	1.7 (0.3 to 3.2)	25	4.3 (1.8 to 6.7)	−2.5 (−6.0 to 0.0)	0.06
Social relatedness	27	2.3 (−1.1 to 5.8)	25	5.0 (1.2 to 8.6)	−2.6 (−7.0 to 2.0)	0.29
Body and object use	27	3.3 (0.3 to 6.2)	25	4.1 (1.5 to 6.7)	−0.9 (−4.4 to 2.7)	0.65
Language	27	0.1 (−1.8 to 2.0)	25	1.6 (−0.2 to 3.5)	−1.5 (−4.0 to 0.9)	0.24
Socialization	27	1.4 (−0.2 to 3.0)	25	2.8 (0.8 to 4.8)	−1.4 (−3.7 to 1.0)	0.28
Total score	27	8.9 (0.2 to 17.6)	25	17.8 (10.3 to 23.2)	−8.9 (−19.4 to 1.6)	0.11
Vineland Adaptive Behavior Scale						
Communication (parent)	28	−1.6 (−5.0 to 1.8)	28	2.1 (−1.2 to 5.5)	−3.7 (−8.2 to 0.8)	0.12
Communication (teacher)	17	0.7 (−3.1 to 4.4)	15	0.6 (−6.6 to 7.8)	0.1 (−2.4 to 2.5)	0.98
Clinical Global Impression Scale						
Response to social interaction	25	−0.2 (−0.9 to 0.5)	24	0.3 (−0.2 to 0.8)	−0.5 (−1.3 to 0.3)	0.24
Social initiation	25	0.2 (−0.2 to 0.7)	24	0.2 (−0.2 to 0.7)	−0.0 (−0.1 to 0.1)	0.97
Use of speech	25	0.2 (−0.2 to 0.6)	24	0.2 (−0.1 to 0.6)	−0.1 (−0.5 to 0.4)	0.72
Types of repetitive behavior	25	−0.1 (−0.6 to 0.4)	24	0.2 (−0.2 to 0.7)	−0.3 (−1.0 to 0.3)	0.32
Behavior problems	25	0.6 (−0.1 to 1.0)	24	0.1 (−0.3 to 0.5)	0.4 (−0.1 to 0.9)	0.13
Activity level	25	0.04 (−0.3 to 0.4)	24	−0.04 (−0.5 to 0.4)	0.1 (−0.4 to 0.6)	0.76
Sleep problems	24	−0.5 (−1.1 to 0.1)	24	−0.2 (−0.7 to 0.3)	−0.3 (−1.0 to 0.4)	0.43
Digestive problems	24	−0.2 (−0.7 to 0.2)	24	−0.2 (−0.6 to 0.2)	−0.1 (−0.6 to 0.4)	0.49

*CI denotes confidence interval.

†The initial sample size for each group was 30. The numbers of children listed reflect reductions due to withdrawal and loss to follow-up (two children in each group) and the fact that data were missing for some children at each evaluation.

secretin carries the additional risk of immunogenicity in humans, we chose to examine the effects of the synthetic form of human secretin.

The lack of positive effects of secretin treatment with respect to any of the features of autism stands in contrast to the anecdotal reports of positive and even dramatic effects that have appeared recently on television, in print, and on the Internet. The widespread circulation of anecdotal reports of the benefits of secretin in the treatment of autism may have raised expectations among parents and care providers and biased them toward perceiving improvement.

Suboptimal or ineffective treatments for autism are often promoted and widely accepted in the absence of empirically validated treatment. In this respect, secretin may become one of the several proposed alternative treatments for autism (others include special diets, vitamin therapy, facilitated communication, and sensory integration) that continue to be used despite a lack of empirical validation.[6,22] We found that most parents remained interested in secretin as a form of treatment for their child's autism even after being told that we found no evidence of benefit. It is important to note that other treatments for autism have been empirically validated. These include direct behavioral instruction to improve social interaction and communication skills[23,24] and behavioral[25] and medical[3,5,26-29] interventions for managing the aberrant types of behavior associated with autism. In summary, we found that a single dose of synthetic human secretin was similar to placebo for the treatment of children with autistic disorders.

REFERENCES

1. Rapin I. Autism. N Engl J Med 1997;337:97-104.
2. Anderson GM, Freedman DX, Cohen DJ, et al. Whole blood serotonin in autistic and normal subjects. J Child Psychol Psychiatry 1987;28:885-900.
3. McDougle CJ, Naylor ST, Cohen DJ, Volkman FR, Heninger GR, Price LH. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. Arch Gen Psychiatry 1996;53:1001-8.
4. Lewis MH, Bodfish JW, Powell SB, Golden RN. Clomipramine treatment for stereotype and related repetitive movement disorders associated with mental retardation. Am J Ment Retard 1995;100:299-312.
5. DeLong GR, Teague LA, McSwain Kamran M. Effects of fluoxetine treatment in young children with idiopathic autism. Dev Med Child Neurol 1998;40:551-62.
6. Nickel RE. Controversial therapies for young children with developmental disabilities. Infants Young Child 1996;8:29-40.
7. Shattock P. Role of neuropeptides in autism and their relationships with classical neurotransmitters. Brain Dysfunction 1991;4:308-19.
8. Beck G, Beck V. Unlocking the potential of secretin: information and questions for parents and physicians who want to learn more about secretin as its use is explored in autism and other disorders. San Diego, Calif.: Autism Research Institute, September 1998.
9. Johannes L. Mother's quest to help autistic child advances, after some odd turns. Wall Street Journal. March 10, 1999:1.
10. Kastner T. Secretin and autism. Except Health Care 1998;9(10):45-6.
11. Horvath K, Stefanatos G, Sokolski KN, Wachtel R, Nabors L, Tildon JT. Improved social and language skills after secretin administration in patients with autistic spectrum disorders. J Assoc Acad Minor Physicians 1998;9:9-15.
12. Kolts BE, McGuigan JE. Radioimmunoassay measurement of secretin half-life in man. Gastroenterology 1977;72:55-60.
13. Christ A, Werth B, Hildebrand P, Gyr K, Stalder GA, Beglinger C. Human secretin: biologic effects and plasma kinetics in humans. Gastroenterology 1988;94:311-6.
14. Diagnostic and statistical manual of mental disorders, 4th ed.: DSM-IV. Washington, D.C.: American Psychiatric Association, 1994.
15. Schopler E, Reichler RJ, Renner BR. The Childhood Autism Rating Scale (CARS) for diagnostic screening and classification in autism. New York: Irvington, 1986.
16. Krug DA, Arick JR, Almond PJ. Autism screening instrument for education planning: an assessment and educational planning system for autism and developmental disabilities. 2nd ed. Examiner's manual. Austin, Tex.: PRO-ED, 1980.
17. Sparrow SS, Balla DA, Cicchetti DV. Vineland Adaptive Behavior Scales. Interview edition: survey form manual. Circle Pines, Minn.: American Guidance Service, 1984.
18. National Institute of Mental Health. CGI (Clinical Global Impression) Scale. Psychopharmacol Bull 1985;21:839-43.
19. Idem. Treatment Emergent Symptoms Scale — write-in (TESS). Psychopharmacol Bull 1985;21:1069-73.
20. Hays WL. Statistics for the social sciences. 3rd ed. New York: Holt, Rinehart & Winston, 1981.
21. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview–Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 1994;24:659-85.
22. Campbell M, Schopler E, Cueva JE, Hallin A. Treatment of autistic disorder. J Am Acad Child Adolesc Psychiatry 1996;35:134-43.
23. Lovaas OI. Behavioral treatment and normal educational and intellectual functioning in young autistic children. J Consult Clin Psychol 1987; 55:3-9.
24. Birnbrauer J, Leach D. The Murdoch Early Intervention Program after two years. Behav Change 1993;10:63-74.
25. Matson JL, Benavidez DA, Compton LS, Paclawskyj T, Baglio C. Behavioral treatment of autistic persons: a review of research from 1980 to the present. Res Dev Disabil 1996;17:433-65.
26. McDougle CJ, Holmes JP, Carlson DC, Pelton GH, Cohen DJ, Price LH. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. Arch Gen Psychiatry 1998;55:633-41.
27. Gordon CT, State RC, Nelson JE, Hamburger SD, Rapoport JL. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. Arch Gen Psychiatry 1993;50:441-7.
28. Kolmen BK, Feldman HM, Handen BL, Janosky JE. Naltrexone in young autistic children: a double-blind, placebo-controlled crossover study. J Am Acad Child Adolesc Psychiatry 1995;34:223-31.
29. Anderson L, Campbell M, Grega DM, Perry R, Small AM, Green WH. Haloperidol in the treatment of infantile autism: effects on learning and behavioral symptoms. Am J Psychiatry 1984;141:1195-202.