

A Randomized, Double-Blind, Placebo-Controlled Trial of Porcine Versus Synthetic Secretin for Reducing Symptoms of Autism

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ABSTRACT

Objective: To compare the effects of a single dose of biologic and synthetic porcine secretin to placebo on a variety of autism symptoms. **Method:** Eighty-five children with autism without other medical conditions and not taking other psychotropic medications participated (ages between 3 and 12 years, IQs ≥ 55). Children were grouped into trios matched by age and IQ and then randomly assigned to one of three treatment groups: biologic secretin (2 CU/kg), synthetic secretin (0.4 $\mu\text{g}/\text{kg}$), and placebo. Measures collected 1 week before and 4 weeks after infusion included autism symptoms, language skills, and problem behaviors, gathered from parents, teachers, and investigators, who were all blind to treatment. Two-factor, repeated-measures analyses of variance (3 treatment levels by 2 repeated measures, pre- and postinfusion) were used to examine efficacy. **Results:** Direct observation measures did not show change over time related to secretin. Parent reports showed an overall reduction of symptom severity for all treatment groups, including the placebo group. One teacher-report measure showed decreases in autism symptoms in the placebo and synthetic secretin groups. **Conclusions:** No evidence that either biologic or synthetic secretin provided amelioration of symptoms beyond placebo was observed. This held true when children with and without gastrointestinal problems were examined separately. *J. Am. Acad. Child Adolesc. Psychiatry*, 2002, 41(11):000–000. **Key Words:** autism, psychopharmacology, secretin.

Autism is a neurodevelopmental disorder affecting 1 out of 1,000 persons which results in chronic and severe psychopathology, characterized by a triad of symptoms including social impairments, communication impairments, and repetitive behavior and restricted interests (American Psychiatric Association, 1994). Horvath et al. (1998) reported behavioral changes in three young boys with autism spec-

trum disorder after they received an intravenous administration of secretin as part of an upper gastrointestinal (GI) endoscopy workup for GI complaints. All children were described as minimally verbal and minimally socially responsive and had received developmental and psychological evaluations at some point before the secretin infusion. Based on notes from therapists and teachers, parent interviews, and videotape records of child behavior, they observed changes in behavior after the procedure. All three patients demonstrated marked social, cognitive, and communicative gains after the initial infusion, as well as improvement in their GI symptoms, and a second infusion carried out some weeks or months later also was followed by additional gains. One of the patients no longer met criteria for a diagnosis of autism at later follow-up. The published findings were reported in the media and resulted in significant interest in secretin as a possible treatment for autism.

Several follow-up controlled studies examining the effects of secretin on symptoms of autism have since been published. Four studies used randomly assigned, double-blind comparisons of secretin-infused versus placebo-

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infused groups. Sandler et al. (1999) examined the performance of 28 synthetic human secretin-treated children with 28 placebo-treated children at two baseline points and five posttreatment points. Children were carefully diagnosed on several measures and represented both the full syndrome and those with milder symptoms (pervasive developmental disorder-not otherwise specified [PDD-NOS]). No group differences were found in communication abilities or symptom severity by parents or teachers on any of the 16 measurements taken. Improvement in both groups was observed in equivalent numbers of children. Dunn-Geier et al. (2000) used a similar design to compare the effects of porcine secretin in 47 children with autism and 48 placebo-treated children. Baseline and 3-week posttreatment measures included a standardized language scale and parent assessment of autism symptoms. Both groups demonstrated some improvements on most measures following infusions, with no difference in the groups. Equivalent numbers of patients demonstrated improvements postinfusion. Coniglio et al. (2001) studied 60 children with autism using porcine secretin and placebo groups with follow-up assessments 3 and 6 weeks postinjection. Although the secretin group showed a marginally statistically significant improvement in autistic behaviors at 3 weeks ($p = .051$), no differences were found 6 weeks after injection. Owley et al. (2001) also studied 56 children randomly treated with either porcine secretin or placebo. After following the children for 8 weeks using both parent-report and observational measures, no differences were found between the secretin and placebo groups.

Two other studies used crossover designs to assess secretin efficacy. Owley et al. (1999) examined effects of porcine secretin for 20 subjects (unique to those in Owley et al., 2001), randomly assigned to secretin or placebo groups initially and then receiving the other substance 4 weeks after the initial infusion. Participants were 3–12 years of age and carefully diagnosed. Measures administered at baseline, 4 weeks, and 8 weeks included direct measures of autism symptoms, adaptive behavior, receptive language, fine motor skills, and general symptoms. No group differences were observed at the 4-week point on any measure, and when all the subjects' data were analyzed to examine their response to secretin versus response to placebo, no group differences were found. Similarly, Corbett et al. (2001) used the same design in a pilot study of porcine secretin for 12 carefully diagnosed subjects aged 4–12. Measures involved symptoms of

autism, an affect measure, and analysis of a language sample, as well as GI symptoms and stool analysis. As with all of these other studies, there was a positive effect on measures after infusion, but the effect was similar to that of placebo and that of secretin for all variables except affect and activity level, which were more improved after secretin than placebo infusion.

Finally, a few studies have examined the role of repeated doses of secretin on autism symptoms. Chez et al. (2000) recently reported a two-part clinical trial of secretin. In the first part, 56 patients (45 of whom were taking other medications) were included, consisting of 34 children with a diagnosis of PDD-NOS and 22 with autistic disorder. Subjects received an open-label trial of a single injection of secretin (2 CU/kg). Parents evaluated child behavior pre- and postinjection with the Childhood Autism Rating Scales, with reports of some parents noting minimal but potentially significant improvements in behavior, language, and GI symptoms. The 17 most responsive patients, and 8 new patients, were then enrolled in a double-blind, placebo-controlled trial. Each group received either secretin or placebo, with crossover at 4 weeks. Follow-up demonstrated few clinically meaningful improvements compared with placebo, though secretin was reported to cause some transient positive changes in speech and behavior in some children. Roberts et al. (2001) randomly assigned 68 children to receive two doses of either placebo or porcine secretin, 6 weeks apart. Assessments of language, cognition, and autistic symptoms were made at baseline and at 1 and 2 weeks after each injection, for a total of five assessments. They found no evidence that two doses of porcine secretin served as an effective treatment for children with autism.

As a result of their findings and a growing number of reports of other GI abnormalities in autism, D'Eufemia et al. (1996), Wakefield et al. (1998), and Horvath et al. (1999) suggested a possible abnormality in the regulation of secretin receptors in the pancreas, hypothesizing a relationship between intestinal symptoms and the child's behavioral problems. Secretin is a polypeptide that contains 27 amino acids. When acid chyme with a pH of less than 4.5 enters the duodenum from the stomach, it causes secretin release into the mesenteric circulation. Secretin stimulates pancreatic bicarbonate secretion, thus raising the pH of the stomach contents in the duodenum. Secretin has been noted to cause increased blood flow to the GI tract but not to the brain. Charlton et al. (1983) noted that when the peptide was injected intravenously into

rats, a decrease in respiration rate occurred. However, when the brain was perfused with secretin, from the lateral ventricle to the cisterna magna, an increase in the respiratory rate occurred. These data, combined with the fact that secretin and secretin binding sites have been identified in the brain, suggest that secretin may be a neurotransmitter or play a neuroregulatory role in the central nervous system.

The present study sought to extend previous research in several ways. First, the sample reported here is substantially larger than those used in previous studies of secretin. Second, we directly compared porcine and synthetic secretin. Third, we included measures from three independent sources: blind observers, parent report, and teacher report. Fourth, we assessed presence of GI symptoms to determine whether response to treatment was related to this factor.

METHOD

Subject Selection

Children between the ages of 3 and 12 years (inclusive) with a *DSM-IV* (American Psychiatric Association, 1994) clinical diagnosis of autism or PDD-NOS (made by a physician or clinical psychologist) were recruited for study. All diagnoses of autism or PDD-NOS were confirmed by administration of the Autism Diagnostic Observation Schedule (ADOS) by trained investigators. Subjects had a nonverbal IQ ≥ 55 as obtained on standardized testing within 3 years of recruitment. Subjects were grouped into trios matched by chronological age (range of 12 months for each group) and Vineland Communication Standard Score (range of 10 *T* score points) before entry into the protocol. Children were then randomly assigned to treatment group. Children were excluded if they had previously received secretin, had any medical condition for which the autism was considered symptomatic (for example, fragile X or tuberous sclerosis), or had comorbid epilepsy. Children receiving any psychotropic drug treatment 6 months prior to recruitment and children with known allergies to pork products were also excluded. This study was approved by the institutional review boards of the University of Colorado Health Sciences Center and the University of Washington. Informed consent was obtained from the parents or guardians of children who participated in this investigation.

Measures

All dependent measures were obtained within 1 week prior to infusion and 4 weeks after infusion.

Autism Diagnosis and Symptoms. The Autism Diagnostic Observation Schedule-Generic (ADOS-G) (Lord et al., 2000) is a semistructured play-based observational assessment used to measure social and communication symptoms in autism. The ADOS-G was administered by trained investigators. A modification of the Secretin Outcome Survey (SOS), developed by Rimland, was used to measure salient autism symptoms and related behaviors. This 42-item questionnaire was completed by the child's parents and a teacher who had regular contact with the child. Subscales include Social (nine items), Communication (six items), Repetitive Behavior (seven items), Digestive Functioning

(six items), Mood (seven items), Sensory (four items), and single items for Hyperactivity, Lethargy, and Sleep Functioning. Adequate reliability for these subscales, observed as internal consistency (Cronbach α), averaged .81 (range .69–.89) for both parent and teacher measures. The exception was the Digestive subscale for the teacher report, which had a reliability of .26. The SOS measure was also completed by the parents at 2 weeks postinfusion in addition to the assessment at 4 weeks.

Language. The Expressive One-Word Picture Vocabulary Test-Revised (Gardener, 1990) assessed expressive vocabulary and required the child to name an object, action, or concept that is illustrated on a card. Although this test provides age-based norms, raw score values were used for the purpose of repeated-measures analyses. The MacArthur Communicative Development Inventory (Words and Sentences version) (Fenson et al., 1993), completed by parents, is designed for children aged 16–30 months, but can be used with older children with delayed speech. The total Vocabulary score from the MacArthur was used for analyses.

Problem Behavior. The Aberrant Behavior Checklist-Community (ABC) version (Aman et al., 1985) is a 58-item symptom checklist for assessing behavior problems in people with developmental disabilities. Subscales include Irritability, Social Withdrawal, Stereotyped Behavior, Hyperactivity, and Inappropriate Speech. The child's parent and teacher completed this measure. As with the SOS, parents completed this measure at 2 weeks postinfusion in addition to the full assessment at 4 weeks.

Secretin Infusions

Infusions were performed according to a double-blind procedure in hospital settings to which the child was naive. All children received a single infusion of either extracted porcine secretin (2 CU/kg), synthetic porcine secretin (0.4 μ g/kg), or an appropriate volume of placebo over 2 minutes intravenously. Children were tested for anaphylactic reactions prior to infusions by administering a test dose (0.1 mL) from the vial from which the treatment infusion was taken. No child had an allergic reaction to any of the preparations.

Follow-up Assessment

One week after the infusion, a telephone interview was conducted with the parent to review the child's clinical status and the SOS rating questionnaire. Follow-up assessment using all measures obtained during baseline were completed at the fourth postinfusion week.

RESULTS

Subjects

Eighty-five of the 90 children initially enrolled in the study completed the study protocol (34 children at the University of Colorado Health Sciences Center and 51 children at the University of Washington). Four subjects discontinued participation: in two the intravenous line could not be properly established and thus the infusion was not given, one decided against the infusion, and one did not return for the follow-up assessment. A fifth child developed illness and fever after the infusion and study personnel and parents were unblinded in the course of treating this illness. This child did complete the study protocol; however, the

TABLE 1
Baseline Measures by Treatment Group

	Biologic Secretin			Synthetic Secretin			Placebo			ANOVA	
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>F</i>	<i>p</i>
Age in months	26	76.5	25.7	26	80.7	29.8	33	78.3	24.9	0.161	.852
Vineland Communication ^a	26	50.0	13.3	26	50.3	10.8	33	51.7	12.1	0.157	.855
ADOS Total	26	15.6	3.0	26	15.8	3.5	33	15.3	3.5	0.148	.863
ADOS Communication	26	5.6	1.7	26	6.0	1.8	33	5.7	2.0	0.291	.748
ADOS Social	26	10.0	2.0	26	9.8	2.3	33	9.6	2.1	0.250	.779
EOW Vocabulary	25	15.2	19.5	26	14.9	17.6	33	14.6	15.1	0.009	.991
MacArthur Vocabulary	24	226.2	242.2	24	225.3	229.4	32	245.9	228.3	0.072	.930
ABC Total—Parent	26	61.4	22.1	25	54.2	24.0	33	58.9	32.0	0.468	.628
SOS Total—Parent	25	4.3	1.5	24	4.4	1.5	33	4.0	1.9	0.444	.643
ABC Total—Teacher	25	54.8	22.3	25	56.4	24.0	28	57.5	20.4	0.099	.906
SOS Total—Teacher	21	4.7	1.3	21	4.7	1.6	28	4.7	1.2	0.015	.985

Note: ADOS = Autism Diagnostic Observation Schedule (Lord et al., 2000); EOW = Expressive One-Word Picture Vocabulary Test (Gardener, 1990); ABC = Aberrant Behavior Checklist (Aman et al., 1985); SOS = Secretin Outcome Survey; ANOVA = analysis of variance.

^a Standard score.

data were not included in the analyses because raters and parents were no longer blind to the treatment this child received. Comparison between the three treatment groups on baseline measures yielded no significant differences on any measures (all *p* values > .10, Table 1).

Comparison of Treatment Groups

Efficacy was examined using repeated-measures analysis of variance (ANOVA) in which the baseline and 4-week assessments were the within-subjects factor (labeled “time”) and treatment group was the between-subjects factor with three levels. Parallel analyses were conducted using random regression models in a multilevel model-

ing context to examine the presence of site effects using HLM and MLWin software. No site effects were observed; thus data from both sites were combined and results from the repeated-measures ANOVA are reported. Measures based on direct observation, including the ADOS-G Communication and Social scores, and expressive one-word vocabulary, did not show any overall change over time, nor any time by treatment interactions (all *p* values > .05, Table 2). The time by treatment interaction is denoted as “treatment” in the following tables.

There was an overall reduction of symptom severity at 4 weeks postinfusion on the parent-report total scores from the ABC ($F_{1,74} = 13.86, p < .001$) and the SOS ($F_{1,75} =$

TABLE 2
Outcome Measures by Treatment Group

	Biologic Secretin			Synthetic Secretin			Placebo			Time (<i>F</i>)	Treatment (<i>F</i>)
	<i>n</i>	Mean Change (95% CI)		<i>n</i>	Mean Change (95% CI)		<i>n</i>	Mean Change (95% CI)			
Observation measures											
ADOS Communication	26	-0.2 (-0.8 to 0.4)		26	-0.2 (-0.8 to 0.5)		33	0.2 (-0.5 to 0.8)		0.13	0.39
ADOS Social	26	0.0 (-0.9 to 0.9)		26	0.0 (-0.9 to 0.9)		33	-0.5 (-1.3 to 0.3)		0.61	0.54
EOW Vocabulary	25	1.2 (-0.4 to 2.9)		26	-0.7 (-2.2 to 0.7)		33	2.1 (0.2 to 4.1)		3.07	2.91
Parent report											
ABC Total	25	-10.6 (-18.9 to -2.3)		23	-5.2 (-10.0 to -0.3)		29	-5.8 (-12.4 to 0.9)		13.86***	0.78
SOS Total	24	-0.5 (-0.9 to -0.1)		23	-0.7 (-1.0 to -0.4)		31	-0.5 (-0.9 to -0.1)		26.76***	0.31
SOS Total (2 week)	21	-0.4 (-1.0 to 0.2)		19	-0.1 (-0.7 to 0.4)		28	-0.5 (-1.1 to 0.0)		4.54*	0.13
MacArthur Vocabulary	21	16.5 (-11.7 to 44.8)		22	12.3 (-5.6 to 30.2)		30	23.4 (9.7 to 37.1)		10.06**	0.38
Teacher report											
ABC Total	22	0.4 (-8.3 to 9.1)		17	-7.9 (-16.1 to 0.3)		26	-12.0 (-18.2 to -5.7)		9.05**	3.18*
SOS Total	18	-0.2 (-1.0 to 0.7)		16	-0.5 (-1.1 to 0.0)		22	-0.6 (-1.3 to 0.1)		4.33*	0.40

Note: ADOS = Autism Diagnostic Observation Schedule; EOW = Expressive One-Word Picture Vocabulary Test; ABC = Aberrant Behavior Checklist; SOS = Secretin Outcome Survey; CI = confidence interval.

26.76, $p < .001$). This observed decrease, however, did not differ as a function of treatment group on either measure ($F_{2,74} = 0.78$, $p = .46$; $F_{2,75} = 0.31$, $p = .74$, respectively).

Examination of the subscales of these measures showed a similar pattern of results (Table 3). The ABC subscales Irritability/Agitation ($F_{1,74} = 10.89$, $p = .001$), Social Withdrawal ($F_{1,74} = 13.95$, $p < .001$), and Hyperactivity ($F_{1,74} = 8.65$, $p = .004$) showed overall decrease in scores, whereas the Stereotyped Behavior and Inappropriate Speech subscales did not show any improvement (p values $> .05$). The SOS subscales Social Behavior ($F_{1,75} = 26.83$, $p < .001$), Communication ($F_{1,75} = 11.11$, $p = .001$), Digestive Functioning ($F_{1,75} = 5.41$, $p = .023$), Sensory

($F_{1,74} = 19.62$, $p < .001$), and Sleep Problems ($F_{1,73} = 6.38$, $p = .014$) showed overall decrease in problem levels whereas Repetitive Behavior and Mood subscales and Hyperactivity and Lethargy items did not. No significant time by treatment interactions were observed for any of the subscales of the ABC or SOS measures; thus there was no evidence of secretin efficacy when specific subscales were examined. Parent reports on the SOS conducted at 2 weeks postinfusion also showed overall decrease in total symptoms ($F_{1,68} = 4.54$, $p = .037$), but no differences by treatment group ($F_{2,68} = 0.13$, $p = .88$).

The teacher-report total score on the ABC was the only overall measure to show a significant time by treatment

TABLE 3
Outcome Subscale Measures by Treatment Group

	Biologic Secretin		Synthetic Secretin		Placebo		Time (<i>F</i>)	Treatment (<i>F</i>)
	<i>n</i>	Mean Change (95% CI)	<i>n</i>	Mean Change (95% CI)	<i>n</i>	Mean Change (95% CI)		
Parent report								
ABC Irritability	25	-2.9 (-5.3 to -0.5)	23	-1.3 (-3.0 to 0.4)	29	-1.5 (-3.4 to 0.5)	10.89***	0.79
ABC Withdrawal	25	-3.5 (-6.2 to -0.7)	23	-1.3 (-3.5 to 0.8)	29	-2.0 (-3.6 to -0.4)	13.95***	1.01
ABC Stereotyped behavior	25	-0.8 (-2.1 to 0.4)	23	0.0 (-0.9 to 0.9)	29	-0.4 (-1.3 to 0.5)	2.13	0.68
ABC Hyperactivity	25	-2.8 (-5.4 to -0.3)	23	-1.7 (-3.7 to 0.3)	29	-2.2 (-5.4 to 0.9)	8.65**	0.17
ABC Inappropriate Speech	25	-0.5 (-1.4 to 0.4)	23	-0.8 (-1.8 to 0.2)	27	0.6 (-0.5 to 1.8)	0.69	2.46
SOS Social	24	-0.4 (-1.2 to 0.3)	23	-1.2 (-1.8 to -0.6)	31	-0.9 (-1.4 to -0.5)	26.83***	1.66
SOS Communication	24	-0.3 (-1.1 to 0.5)	23	-0.8 (-1.5 to 0.0)	31	-1.0 (-1.7 to -0.4)	11.11**	1.09
SOS Repetitive Behavior	24	-0.1 (-1.1 to 0.9)	23	-0.7 (-1.5 to 0.1)	31	0.0 (-0.6 to 0.6)	1.49	0.91
SOS Digestive	24	-0.3 (-0.8 to 0.1)	23	-0.3 (-0.8 to 0.3)	31	-0.4 (-0.8 to 0.1)	5.41*	0.05
SOS Mood	23	-0.4 (-0.9 to 0.1)	23	-0.2 (-1.0 to 0.5)	31	-0.2 (-1.0 to 0.5)	2.16	0.07
SOS Sensory	23	-1.3 (-2.2 to -0.4)	23	-1.3 (-1.9 to -0.7)	31	-0.5 (-1.3 to 0.4)	19.62***	1.64
SOS Hyperactivity	23	-0.1 (-1.2 to 1.1)	23	-0.8 (-2.1 to 0.5)	31	-0.3 (-1.2 to 0.7)	1.52	0.47
SOS Lethargy	23	-0.1 (-1.2 to 0.9)	23	-0.1 (-1.1 to 0.9)	30	-0.3 (-1.0 to 0.4)	0.61	0.08
SOS Sleep	23	-0.7 (-1.7 to 0.3)	22	-1.0 (-2.1 to 0.2)	31	-0.9 (-2.2 to 0.3)	6.38*	0.08
Teacher report								
ABC Irritability	22	0.7 (-2.4 to 3.7)	17	-1.4 (-4.0 to 1.3)	26	-1.5 (-4.2 to 1.3)	0.79	0.80
ABC Withdrawal	22	-0.5 (-2.7 to 1.6)	17	-4.1 (-6.9 to -1.3)	26	-4.4 (-6.6 to -2.2)	20.30***	3.63*
ABC Stereotyped Behavior	22	-0.6 (-2.2 to 1.0)	17	-0.5 (-2.1 to 1.0)	26	-1.6 (-2.8 to -0.5)	5.37*	0.89
ABC Hyperactivity	22	1.1 (-2.5 to 4.6)	17	-1.7 (-4.7 to 1.3)	26	-3.7 (-6.0 to -1.3)	2.99	3.04
ABC Inappropriate speech	22	-0.2 (-1.4 to 1.0)	17	-0.2 (-1.0 to 0.7)	26	-0.8 (-1.5 to 0.0)	2.02	0.59
SOS Social	18	-0.3 (-1.0 to 0.5)	16	-0.8 (-1.7 to 0.0)	22	-1.0 (-2.0 to -0.1)	8.75**	0.92
SOS Communication	18	0.0 (-1.1 to 1.0)	16	0.1 (-1.1 to 1.4)	22	-1.0 (-1.8 to -0.2)	1.30	1.83
SOS Repetitive Behavior	18	0.6 (-0.5 to 1.6)	16	-0.8 (-1.7 to 0.2)	22	-0.4 (-1.1 to 0.4)	0.63	2.35
SOS Digestive	10	0.0 (-0.5 to 0.4)	10	-0.9 (-1.9 to 0.1)	15	-1.0 (-2.5 to 0.4)	4.13	0.94
SOS Mood	14	-0.1 (-0.9 to 0.8)	15	-0.2 (-0.9 to 0.6)	18	-0.7 (-1.6 to 0.3)	1.55	0.65
SOS Sensory	14	-1.0 (-2.6 to 0.7)	14	-0.6 (-2.1 to 0.9)	18	-0.8 (-1.9 to 0.3)	4.18*	0.07
SOS Hyperactivity	13	0.5 (-0.5 to 1.6)	14	-0.1 (-1.4 to 1.2)	16	-0.2 (-2.3 to 1.9)	0.05	0.25
SOS Lethargy	12	-0.5 (-1.6 to 0.6)	14	-0.7 (-1.9 to 0.5)	15	-1.2 (-2.4 to 0.0)	6.49*	0.44

Note: ABC = Aberrant Behavior Checklist; SOS = Secretin Outcome Survey; CI = confidence interval.

* $p < .05$; ** $p < .01$; *** $p < .001$.

interaction ($F_{2,62} = 3.18, p = .049$); however, this was due to the synthetic secretin and the placebo group showing a decrease in problem behaviors (change of -7.9 , 95% confidence interval [CI] -16.1 to 0.3 ; change of -12.0 , 95% CI -18.2 to -5.7 , respectively) while the biologic secretin group did not (change of 0.4 , 95% CI -8.3 to 9.1). Analysis of the subscales of this measure showed significant time by treatment interactions on the Social Withdrawal scale ($F_{2,62} = 3.63, p = .032$), with the same pattern of synthetic secretin (-4.1 , 95% CI -6.9 to -1.3) and placebo (-4.4 , 95% CI -6.6 to -2.2) showing a decrease and biologic secretin showing no change (-0.5 , 95% CI -2.7 to 1.6). The teacher-report total score on the SOS did show a significant overall change over time ($F_{1,53} = 4.33, p = .042$), but no difference as a function of treatment group ($F_{2,53} = 0.40, p = .68$).

Subgroup Analyses

Analyses were repeated with various subgroups of the original sample in order to test the hypothesis that secretin efficacy is limited to a narrower population than that represented by the whole sample. Four subgroups were created on the basis of the following criteria: (1) only those children whose standard score on the Vineland Communication scale was less than 60, (2) children younger than 72 months, (3) children with reported GI problems, and (4) those with no reported GI problems. The sample sizes

for these subgroups are presented in Table 4. Results from these subgroup analyses parallel those for the whole sample. Several measures showed an overall improvement in scores; however, none of these measures showed differential change in symptoms as a function of treatment group within any of the subgroups examined.

Conclusion

There was no evidence that either biologic secretin or synthetic secretin demonstrated an amelioration of symptoms beyond that observed in the placebo group. When analyses were repeated using subgroups of the original sample—those with Vineland Communication scores less than 60, children younger than 72 months, and those with and without GI problems—the results were similar with no evidence of secretin efficacy found.

DISCUSSION

This study benefited from using a relatively larger sample, more restrictive selection criteria, more rigorous matching, and exclusion of children with comorbid neurological illness or active psychotropic treatment. In addition, this was one of the few secretin effectiveness studies to use multiple informants, including parents, teachers, and investigators, and to examine separately children with GI symptoms. Nevertheless, our findings replicate those of previous investigators, indicating that secretin does

TABLE 4
Subgroup Analyses of Outcome Measures by Treatment Group

	Subgroup							
	Vineland Communication <60 (<i>n</i> = 21, 21, 24) ^a		Age <72 Months (<i>n</i> = 12, 13, 16)		Current GI Problems (<i>n</i> = 10, 11, 10)		No Current GI Problems (<i>n</i> = 16, 15, 23)	
	Time	Treatment	Time	Treatment	Time	Treatment	Time	Treatment
Observation measures								
ADOS Communication	0.01	0.73	1.48	0.01	0.01	2.45	0.05	0.23
ADOS Social	0.10	0.35	0.27	2.46	1.35	0.09	2.55	0.66
EOW Vocabulary	1.74	1.09	0.60	0.74	0.23	1.00	2.70	1.89
Parent report								
ABC Total	11.66**	0.20	4.78*	0.28	4.54*	1.81	8.83**	0.31
SOS Total	18.25***	0.16	4.10	0.98	9.72**	0.36	17.83***	0.86
SOS Total (2 week)	4.80*	0.41	2.20	0.98	0.85	0.37	4.43*	0.03
MacArthur Vocabulary	3.18	0.51	12.93**	0.14	8.69**	0.04	3.35	0.42
Teacher report								
ABC Total	8.18**	2.32	3.99	0.39	0.18	2.72	17.25***	1.83
SOS Total	3.27	0.31	1.62	0.17	0.91	1.03	3.19	0.04

Note: Results are *F* values ADOS = Autism Diagnostic Observation Schedule; EOW = Expressive One-Way Picture Vocabulary Test; ABC = Aberrant Behavior Checklist; SOS = Secretion Outcome Survey; GI = gastrointestinal.

^a Sample size for biologic secretin, synthetic secretin, and placebo groups, respectively.

* $p < .05$; ** $p < .01$; *** $p < .001$.

not affect the symptoms or behaviors associated with autism spectrum disorders. None of the informant groups, including parents, reported positive effects of secretin on autistic behavior that were specifically related to secretin.

The placebo response rate in the present study, and in other studies of children with autism, is worth noting. The effect sizes of these expectancy effects on the total score measures were 0.18 (ABC) and 0.26 (SOS) for parent report and 0.59 (ABC) and 0.50 (SOS) for teacher report. Other studies have found similar expectancy effects. Dunn-Geier et al. (2000) observed an effect size of 0.52 for placebo using the parent-report Autism Behavior Checklist (Krug et al., 1993) total score, and Coniglio et al. (2001) observed an effect size of 0.76 for placebo using the Gilliam Autism Rating Scale Autism Quotient score (Gilliam, 1995). Measures based on direct observation of child behavior have tended to have smaller expectancy effects. The caveat is that direct observation measurements are based on a much narrower sample of behavior than ratings provided by parents and other caregivers and thus may not detect important clinical improvement present in other settings. No single measurement can address the limitations of expectancy effects on the one hand and a limited behavioral context on the other; this highlights the importance of a multifaceted assessment of intervention effects. Researchers investigating the efficacy of interventions with children with autism must continue to focus on these issues and be aware of the difficulties present in teasing out significant treatment effects from expectancy effects.

Limitations

Although this study did examine subgroups of children based on GI functioning, age, and communication level, sample heterogeneity remains a potential explanation for a failure to identify significant effects. At the time of this study, the state of the science does not permit any means to reliably segregate clinically meaningful subgroups, particularly those based on reliably measured biologic variables. Furthermore, this study was based on a single infusion of secretin and cannot be generalized to effect of multiple infusions of secretin.

Clinical Implications

The primary implication of this study is that secretin does not appear to be effective in reducing the symptoms of autism. Although there currently does not exist compelling evidence for the use of secretin for the treatment of autism, there is the possibility that different dosing

regimens may be effective and/or that certain as-yet-undefined subgroups may be responsive. Given the complexity of autism and its treatment and our insufficient understanding of the mechanisms underlying this disorder, clinicians are left with empirical treatments aimed at symptom reduction through more traditional psychological or pharmacological tools.

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