Open-Label Study of Olanzapine Efficacy for Social Impairments in Children with Autism Spectrum Disorder

Julia M. Robertson, M.D.*, Joseph Hagan, M.T. (A.S.C.P.),**

Ann Derrick, A.R.N.P.[+], Stephen Looney, Ph.D.[#],

Patricia Williams, M.D.[++], Peter Tanguay, M.D.[+]

University of Louisville

Departments of Psychological and Brain Sciences *,

Bioinformatics and Biostatistics,**

Psychiatry [+], and Pediatrics [++]

Louisville, Kentucky

Louisiana State University Health Sciences Center

Department of Public Health and Preventive Medicine[#]

Reprint requests:

Julia M. Robertson, M.D.

Department of Psychological and Brain Sciences

University of Louisville

Louisville, Kentucky 40292

Acknowledgement: Funding for this study was provided by Lilly Research Laboratories, a division of Eli Lilly and Company, Grant No. F1D-US-X183.

ABSTRACT

Objective: This study was designed to evaluate the efficacy of olanzapine in improving the core social impairments of autism spectrum disorder in children. **Method:** A DSM-IV diagnosis of autism, Asperger's disorder, or PDD-NOS was established in 11 children between the ages of 4 and 11 years (inclusive) using the ADI-R and ADOS-G diagnostic algorithms. Core social deficits in autism were measured before and after eight weeks of open-label olanzapine in the 10 children who completed the study. Scores on three domains of social communication (*Affective Reciprocity*, *Joint Attention*, and *Theory of Mind)* derived from the ADOS and the sum of these three scores (*Total Social Communication*) were the primary outcome measures. Scores on the communication and social relatedness subscales of the ADOS-G diagnostic algorithm; Vineland Socialization, Communication, and Maladaptive Behavior domains; Aberrant Behavior Checklist; Y-BOCS; and CGI were also measured before and after the 8-week trial. **Results:** Significant improvements were observed on the ADOS-G and Vineland for core social and communication deficits as well as for maladaptive behaviors associated with autism. **Conclusion:** Double-blind placebo-controlled studies of the efficacy of olanzapine in improving the core and associated symptoms of autism spectrum disorder in children are warranted.

Key words: autism, PDD-NOS, social communication, ADOS-G, olanzapine

INTRODUCTION

Autism is a neurodevelopmental syndrome defined by deficits in social reciprocity, communication skills, and by restricted and repetitive behaviors and interests (APA 2000). Longitudinal, epidemiological, and family studies support the concept of a spectrum of autism-related disorders [Lord et al. 2000a]. While autism was found to be one of the most robust diagnoses in DSM-IV field trials, a number of cases were identified that did not meet full criteria for autism but appeared to belong in the diagnostic category [Volkmar et al. 1994]. Those subjects were assigned a sub-threshold diagnosis of Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) or "atypical autism" [Tanguay 2000]. The prevalence of this broader autism spectrum may be as high as one per 200-250 school-aged children **[**Tanguay 2000, Volkmar 1991**].**

Haloperidol has been shown in double-blind, placebo-controlled trials to reduce withdrawal, stereotypies, anger, emotional lability, and hyperactivity in children with autism [Anderson et al. 1989, Campbell et al. 1999]. The use of haloperidol is limited, however, by its significant risk of causing drug-related dyskinesias [Campbell et al. 1997]. Atypical antipsychotic drugs have been considered in the treatment of autism because of reports of a decreased risk of extrapyramidal side effects with these agents [Campbell et al. 1999, Tollefson et al. 1997].

Malone [Malone et al. 2001] reported a similar rate of response for each drug in a study comparing the efficacy of olanzapine with that of haloperidol in reducing the behavioral abnormalities characteristic of autistic children. Double-blind, placebo-

controlled studies of risperidone have shown this medication to be superior to placebo in reducing aggression, and mood abnormalities in adults [McDougle et al. 1998] and children [McCracken et al. 2002] with pervasive developmental disorders.

The efficacy of risperidone in reducing common behavioral problems associated with autism is well established. In contrast, there are no randomized double-blind studies evaluating the efficacy of olanzapine in improving symptoms of autism in adults or children. Several open trials of olanzapine, however, have raised the intriguing possibility that olanzapine can improve core social and communication symptoms of autism in addition to the associated behavioral problems shown to respond to risperidone.

Potenza [Potenza et al. 1999] used the Ritvo-Freeman Real-Life Rating Scale to measure changes in social and communication skills with olanzapine therapy in individuals diagnosed with one of the pervasive developmental disorders. Significant improvements were observed in social relatedness, emotional responsiveness, and language usage. These improvements were not seen in the controlled trial of risperidone by McDougle [McDougle et al. 1998] which also used the Ritvo-Freeman scale. Improved social relatedness and communication skills with olanzapine administration were also found by a group of researchers from the Netherlands who used the Observer-Video Tape Analysis System to rate pre- and post-drug ADOS interviews [Kemner et al. 2002].

No FDA-approved medications specific for the treatment of the deficits in social relatedness and communication in autism exist. [Cook and Leventhal 1995, Tanguay 2000, Volkmar 2001]. A number of investigators have suggested that controlled studies of olanzapine in the treatment of the core symptoms of autism are warranted based on

preliminary reports of its efficacy. [Campbell et al. 1999, Kemner et al. 2002, Malone et al. 2001, Potenza et al. 1999]. Until recently, however, a method for quantitatively measuring changes in social communication in autism after therapeutic interventions was elusive.

Our goal was to investigate changes in the core social deficits of autism, after a trial of olanzapine, using a rating method specifically designed to measure changes in social communication. This study was designed to examine the effects of olanzapine on domains of social communication handicap [*Affective Reciprocity*, *Joint Attention*, *Theory of Mind, Total Social Communication*] in autistic children using a recently developed dimensional classification system [Robertson et al. 1999, Tanguay et al 1998]. The hypothesis was that an eight-week open-label trial of olanzapine would result in significant improvements in some or all of these social communication domains as measured on the ADOS-G. We hoped to provide solid evidence one way or the other as to whether double-blind placebo-controlled trials of olanzapine as a pharmacological agent specifically targeting the deficits in social relatedness and communication of autism are warranted.

METHODS

Subjects

Children recruited from a larger study of social communication in autism were evaluated with the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al. 1994) and the Autism Diagnostic Observation Schedule-Generic (ADOS-G) (Lord et al. 2000b). Only those children who met DSM-IV criteria for autism, Asperger's disorder, or PDD-NOS (APA 1994) were enrolled. Other inclusion requirements were age between 4 and 12 years; anxiety, irritability, aggression, or hyperactivity of sufficient severity to warrant pharmacologic intervention; and an estimated IQ of 50 or higher. Children with seizure disorders, chromosomal abnormalities, systemic illnesses, or a history of previous olanzapine treatment were excluded from the study, as were those children who required other psychotropic medications during the study period.

Measures

Changes in ADOS-G scores for three domains of social communication handicap (*Affective Reciprocity*, *Joint Attention*, and *Theory of Mind)* and their sum (*Total Social Communication*) were the primary outcome measures. These domains were derived from a factor-analytic study of all variables describing social communication in an earlier version of the ADOS-G (Robertson et al. 1999). A Total Social Communication score was derived by adding the scores on the three individual domains.

The ADOS-G (Lord et al. 2000b) is a semi-structured interview designed to assess severity of autistic symptoms in order to make a diagnosis of autism or PDD-NOS.

A series of standardized social presses is used to evaluate the child's social and communication capacities. Items describing various behaviors related to autism are scored on a scale between 0 (normal), and 3 (highly abnormal).

The ADOS-G interviews were administered and videotaped by two members of the research team fully trained in the use of both the ADI-R and the ADOS-G. To assure consistency, all ADOS-G interviews were administered by one member (A.D.) and videotaped by the other (J.R). To maintain reliability, each of these two investigators independently rated each interview. Ratings were then compared and differences in variable scores were resolved through consensus discussions and, when necessary, joint review of the videotapes.

A diagnostic algorithm (Lord et al. 2000b) from the ADOS-G provided a second measure of changes in social and communication deficits before and after olanzapine. This algorithm is designed to determine whether the individual meets full diagnostic criteria for autism, or for the sub-threshold diagnosis of PDD-NOS. It consists of two subscales: Social Relatedness and Communication. Cut-off scores for autism and for pervasive developmental disorder are provided for each subscale and for the sum of the two subscales.

Additional behavioral rating scales were administered as secondary outcome measures. The Socialization, Communication, and Maladaptive Domains of the Vineland Adaptive Behavior Scales [Vineland] (Sparrow et al. 1984); the Aberrant Behavior Checklist-Community Version (ABC-CV) (Aman 1994)**;** the Compulsive subscale of the Yale-Brown Obsessive Compulsive Scale **(**Y-BOCS) (Goodman et al. 1989); and the Clinical Global Impressions Scale (CGI) (Guy 1976) were administered at baseline and

biweekly throughout the study. The CGI was used to rate overall behavior rather than severity of autism per se.

Baseline physical assessments included a complete physical and neurological examination, Abnormal Involuntary Movement Scale (AIMS), Simpson Angus scale (SAS) (Campbell and Palij 1985), EKG, complete blood count (CBC), comprehensive metabolic panel (CMP), and serum prolactin level. All physical assessments were repeated at the end of the study.

Design

The study was approved by the institutional review board for human subjects at the University of Louisville. Written informed consent was obtained from parent(s) after the study procedures were explained. Written assent was also obtained from those children aged seven and older who were able to reasonably comprehend a simplified explanation of the protocol.

The active treatment phase lasted eight weeks. After completion of all baseline assessments olanzapine was started at a dose of either 2.5 mg or 5 mg every other night, depending on the child's weight and overall physical status. Subjects were clinically evaluated for treatment response, adverse effects, and concomitant medications, and their olanzapine dosages were adjusted, on a weekly basis during the first four weeks of olanzapine treatment, then biweekly for the remainder of the study. Physical assessments at each visit included blood pressure, pulse, weight, AIMS, and SAS.

Data Analysis

The paired t-test was used to test for significant changes between baseline and protocol completion. Pearson's correlation coefficient was used to examine the association between pairs of continuous variables. A time-trend analysis was performed using repeated measures multiple comparisons to determine the first time point at which statistically significant improvement vs. baseline occurred for each secondary outcome measure. All statistical tests were two-tailed and $p < 0.05$ was used as the criterion for statistical significance.

RESULTS

Subject Characteristics

The mean age of the 10 study subjects who completed the trial was 84.1 months (SD=29.6) with a minimum age of 50 months and a maximum age of 143 months. An eleventh subject [male, 6 years old, diagnosis of autism] was enrolled in the study but dropped out after one dosage of olanzapine due to complaints of sedation and problems with transportation. Of the ten completers, there were 9 males and 1 female with 8 Caucasian and 2 African-American. The frequencies for baseline diagnoses according to ADI-R and ADOS–G test results were autism (n=8), Asperger's disorder (n=1), and PDD-NOS (n=1). Subjects were placed into one of five categories according to language ability. The language ability categories were normal language (n=1), some phrase speech (n=3), more than five single words (n=2), less than five single words (n=3), and no words (n=1).

The final daily dosage of olanzapine ranged from 5 mg to 20 mg a day with a mean dosage of 10.75 mg (SD=4.57). The Pearson correlation coefficient did not show a significant association of the final dosage of olanzapine with baseline weight (r=0.328, p=0.354), baseline Total Social Communication score (r=0.058, p=0.874) or change in Total Social Communication (r=-0.214, p=0.552).

Pre-drug Versus Post-drug Comparisons for Primary Outcomes

A paired t-test was performed before and after treatment with olanzapine to examine differences between scores on the three domains of social communication

handicap. There were statistically significant improvements in Affective Reciprocity, Joint Attention, and Total Social Communication scores (Table 1). Paired t-tests were also used to examine changes before and after olanzapine treatment on the ADOS-G diagnostic algorithm scores. The Social Relatedness subscale and the Communication + Social Relatedness subscale showed statistically significant improvement (Table 2). The Pearson correlation between baseline ADOS-G Total Social Communication score and baseline ADOS-G diagnostic algorithm score for Communication + Social Relatedness was not statistically significant (r=0.204, p=0.571). The post-drug correlation for these variable scores was significant (r=0.638, p=0.047).

Predictors of Improvement in Primary Outcome Measures

The correlation between predictor variables and improvement on scores for ADOS-G outcomes was also examined. The predictor variables considered were age, gender, ethnicity, language ability, and diagnosis. There was a statistically significant negative correlation between post-drug numerical improvement on the Affective Reciprocity social communication domain score of the ADOS-G and a pre-drug diagnosis of autism using both the ADI-R and ADOS-G diagnostic algorithms (r = -0.649, p = 0.042). There was a significant positive correlation between improvement on both the Affective Reciprocity (r = 0.645, p = 0.044) and Joint Attention (r = 0.666, p = 0.036) domains and the language category of " some phrase speech". None of the other predictor variables examined showed a significant association with improvement as measured by the ADOS–G domain scores.

Pre-drug Versus Post-drug Comparisons for Secondary Outcomes

Analyses of the secondary outcome measures were performed to examine changes between pre-drug and post-drug values [Table 3]. The secondary outcomes examined were the Socialization, Communication, and Maladaptive Behavior Domains of the Vineland Adaptive Behavior Scales, the five subscales of the Aberrant Behavior Checklist-Community Version (ABC-CV), the Compulsive subscale of the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), and the Clinical Global Impressions Scale (CGI). The mean scores for every secondary outcome showed statistically significant improvement after olanzapine treatment with the exception of the Excessive Speech subscale of the ABC-CV, which just missed the cutoff for statistical significance (Table 3).

Time-Trend Analyses for Secondary Outcomes

A time trend analysis was performed to assess improvement over time for the mean scores on all of the secondary outcome measures (Figures 1-6). Lower scores are better for all of these scales except for the Vineland Communication and Socialization domains, for which a higher score is better. At the week 2 assessment, significant improvement had occurred in scores on all three domains of the Vineland Adaptive Behavior Scales (Figures 1-3): Socialization ($F=10.363$, $df = 1,9$, $p=0.011$), Communication ($F=21.763$, $df = 1,9$, $p=0.001$), and Maladaptive Behavior ($F=13.450$, $df = 1,9$, $p=0.005$).

The subjects' mean scores for all five ABC-CV subscales changed significantly during the course of the study. Two ABC sub-scales showed significantly improvement

by the week 2 assessment: Stereotypies (F=5.828, df = 1,9, p=0.039) and Hyperactivity (F=8.197, df = 1,9, p=0.019). At the week 4 assessment, significant improvement had occurred in scores on two additional ABC subscales: Lethargy (F=9.221, df=1,9, p=0.014) and Irritability (F=7.160, df = 1,9, p=0.025). ABC-total (F=17.939, df = 1,9, p=0.002) (Figure 4), and CGI-Improvement (F=9.000, df = 1,9, p=0.015) (Figure 5) were also significantly improved by the week 4 assessment.

At the week 6 assessment, significant improvement was noted in the ABC Excessive Speech subscale (F=6.688, df = 1,9, p=0.029) and CGI-Severity (F=21.000, df = 1,9, p=0.001) [Figure 6]. Scores on the Y-BOCS compulsive sub-scale did not show significant improvement until week 8 (F=7.750, df = 1,9, p=0.021).

ADOS-G Social Communication Domain Scores versus Vineland Socialization Scores

Spearman correlations between ADOS-G social communication scores and Vineland Socialization scores were examined (Table 4). The post-drug ADOS-G Affective Reciprocity scores were significantly correlated with the post-drug Vineland Socialization scores. Post-drug ADOS-G Joint Attention scores were also significantly correlated with the post-drug Vineland Socialization scores. The ADOS-G Total Social Communication scores significantly correlated with the Vineland Socialization scores at both the pre- drug and post-drug assessments. The same patterns of significant correlations were observed when the Age-Equivalent versions of the Vineland domains were used (Table 4).

Change in ADOS-G Social Communication Scores versus Change in Vineland Socialization Scores

Spearman correlations between improvement in ADOS-G Social Communication Scores and improvement in Vineland Socialization scores were also calculated (Table 5). The correlations were only calculated for domains that changed significantly when comparing pre-drug and post-drug values (see Tables 1 and 2). The change was calculated for all assessments by subtracting the pre-drug scores from the post-drug scores. The correlation between change in Affective Reciprocity and change in Vineland Socialization scores was statistically significant. The correlation between change in Total Social Communication scores and Vineland Socialization scores was also statistically significant. The same patterns of significant correlations were observed when the Age-Equivalent versions of the Vineland were used (Table 5).

ADOS-G Diagnostic Algorithm Scores Versus Vineland Domain Scores (Including Age-Adjusted Scores)

The Spearman correlation was used to examine the association between ADOS-G diagnostic algorithm scores and the Vineland counterpart scales (Table 6). Two of the correlations were statistically significant: the post-drug correlation of the ADOS-G algorithm score for Social Relatedness with the Vineland Socialization domain and the post-drug correlation of the ADOS-G algorithm score for Communication + Social Relatedness with the sum of the Vineland Socialization + Communication domains.

Pre-Drug Versus Post-Drug Test Comparisons for Physical Data

Comparisons of the mean post-drug versus pre-drug values for weight, serum prolactin level, serum glutamic-pyruvic transaminase [SGPT] level, and platelet count showed the only significant changes in physical parameters. Subjects' mean weight increased 4.7 kg (SD=1.5) over the course of the study ($p<0.001$). Basal metabolic indices [BMIs] and age-adjusted BMI percentiles [CDC 2000] pre- and post-study were calculated for the eight subjects for whom a height measurement was available. Mean BMI increased from XX.X [SD, p] to XXX [SD, p]. The highest post-drug BMI was 22.5. Age-adjusted BMI percentiles changed from a pre-study mean of XX.X % [SD, p =] to XX.X % at study completion Four subjects had post-study age-adjusted BMIs of > 100%. No significant changes were noted in serum glucose levels.

Baseline prolactin levels were within normal limits [normal range 1.6 – 18.8 ng/ml] for all subjects. Prolactin levels showed statistically significant increases post-trial with a mean increase of 14.4 ng/ml (SD=5.5) ($p<0.001$). At the end of the trial, seven subjects had elevated prolactin levels. None showed any signs or symptoms of galactorrhea or gynecomastia. Significant changes in platelet count and SGPT were also observed at study completion. Mean platelet count [normal range = 130- - 400 X 10^3/cm] increased 49.2 [SD, p = 0.004], and mean SGPT [normal range 30 – 65 IU/L] increased 7.2 IU/L [SD, p = 0.030]. Post study means for SGPT and platelet count remained within normal limits.

DISCUSSION

Efficacy

This study was designed to determine whether measurable changes in social communication would be observed in a sample of children diagnosed with one of the autism spectrum disorders after an 8-week open-label olanzapine trial. Our hypothesis was that positive changes would occur in one or more of three social communication domains derived from two recent factor-analytic studies of structured diagnostic interviews for autism [Robertson et al. 1999, Tanguay et al 1998]. Due to the tentativeness of this dimensional approach to measuring social communication deficits with the ADOS-G, several well-established methods of measuring social and communication deficits in autism were also used.

The primary outcome measures, scores on three domains of social communication handicap measured by the ADOS-G, showed significant positive changes in Affective Reciprocity, Joint Attention and Total Social Communication at the end of the 8-week trial. Significant positive changes were also observed on the ADOS-G diagnostic algorithm and on the relevant Vineland Domains. Finally, significant improvements were observed on almost all ratings of behavioral abnormalities associated with autism for which haloperidol and risperidone have been shown effective.

The strength of this study lies with the use of multiple assessment instruments known to be effective measures of the core and associated symptoms characteristic of individuals with autism. [Carter et al. 1998, Cook and Leventhal 1995; Lord et al. 1994,

Lord et al. 2000b]. The positive correlations between post-drug ADOS-G social communication scores and post-drug Vineland domain scores lend support to this dimensional approach to measuring social communication deficits in autism.

Safety

A significant increase in mean serum prolactin levels was observed at study completion. Increases in serum prolactin have been reported in children [Wudarsky et al. 1999; Alfaro et al. 2002] and adults [Turrone et al. 2002, Wirshing et al. 2000] receiving both typical and atypical antipsychotic agents. The long-term significance of asymptomatic prolactinemia is unknown [Alfaro et al. 2002]. Studies with longer periods of monitoring serum prolactin on larger samples of children receiving atypical antipsychotic agents are needed to determine the safety of these drugs in children [Wudarsky et al. 1999].

Significant weight-gain also occurred during the eight-week trial. Weight-gain has been observed in autistic children treated with olanzapine [Malone et al. 2001, Potenza et al. 1999] and with risperidone [Hellings et al. 2001; Martin et al. 2004, McCracken et al. 2002]. Amantidine has been found effective in stabilizing psychotropic-induced weight gain in children [Gracious et al. 2002] and adults [Floris et al. 2001]. After completion of this study, amantadine was successful in stabilizing weight in the majority of the children who continued to receive olanzapine.

Significant changes in mean SGPT and mean platelet concentration were observed at the end of the olanzapine trial, but both values remained within normal range. Asymptomatic, transient elevations of liver transaminases have been reported with the

use of olanzapine [Barnes and McPhillips 1999, Kumra et al. 1998]. No reports were found in the literature regarding olanzapine-induced thrombocytosis.

Limitations

The subjects for this study were recruited from a larger project examining social communication in high-functioning autistic children. Moreover, an estimated IQ of greater than 50 was a required criteria of enrollment. Thus, the sample is not representative of the broader spectrum of children with autism who might benefit from a trial of olanzapine. Generalization of the findings is also limited by the small sample size, short protocol length, and open-label study design. No information is provided from this study about the long-term effectiveness and safety of olanzapine in this population. In light of reports of the negative effects of atypical antipsychotic medications on carbohydrate [Haupt and Newcomer 2001, Koller et al. 2001, Wirshing et al. 2000] and lipid metabolism [Koro et al. 2002, Meyer 2001], measurement of pre- and post triglyceride levels, and results from pre- and post-glucose-tolerance tests would have provided valuable additional information about the safety of olanzapine for children with autism.

Clinical Implications

The findings of this study provide additional support for the judicious use of olanzapine in some children with autism spectrum disorders. A small sample of children with moderate autistic psychopathology and substantial behavioral problems showed

significant improvements in social and communication skills and in irritable, withdrawn, hyperactive, stereotypic, and other maladaptive behaviors associated with autism.

The parents of all 10 children who completed this study chose to continue their children on olanzapine after study completion. Each parent felt that the improvements in behavior and social relatedness were more important than the weight problem. It will be important to discuss the risk of weight gain and the unknown risks of elevated serum prolactin levels with parents and children before prescribing olanzapine to children with autism.

Carefully designed double-blind placebo-controlled studies of olanzapine to specifically target the core social and communication deficits of children with autism are warranted based on these results. Protocols designed to evaluate the efficacy of olanzapine in improving social relatedness over longer time periods in autistic children with a broader range of intellectual functioning will contribute valuable information regarding the benefits and safety of its use in this population. Incorporating the use of amantadine into the study design could prevent or reduce the weight gain observed in this and other studies of atypical antipsychotic agents in children. Longitudinal monitoring of prolactin levels during treatment with olanzapine will provide essential information about the long-term effects, if any, of the drug-induced elevations in serum prolactin levels.

REFERENCES

Alfaro CL, Wudarsky M, Nicolson R, Gochman P, Sporn A, Lenane M, Rapoport JL (2002), Correlation of antipsychotic and prolactin concentrations in children and adolescents acutely treated with haloperidol, clozapine, or olanzapine. *J Child Adolesc Psychopharmacol* 12:83-89

Aman M (1994), *Aberrant Behavior Checklist: Community Version*. East Aurora, NY: Slosson Educational Publications

American Psychiatric Association (2000), *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision [DSM-IV-TR]*. Washington DC: American Psychiatric Association

American Psychiatric Association (1994), *Diagnostic and Statistical Manual of Mental Disorders, 4th edition [DSM-IV]*. Washington DC: American Psychiatric Association

[Anderson LT, Campbell M, Adams P, Small AM, Perry R, Shell J [1989], *The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children*. J Autism Dev Disorder 19:227-239] probably removed text reference

Barnes TRE, McPhillips MA [1999], Critical analysis and comparison of the side-effect and safety profiles of the new antipsychotics. *Br J Psychiatry* 174 suppl 38: 34-43

Campbell M, Palij M (1985), Measurement of untoward effects including tardive dyskinesia. *Psychopharmacol Bull* 21:1063-1082

Campbell M, Armenteros JL, Malone RP, Adams PB, Eisenberg ZW, Overall JE [1997], Neuroleptic-related dyskinesias in autistic children: a prospective, longitudinal study. *J Am Acad Child Adolesc Psychiatry*, 36:835-843

Campbell M, Rapoport JL, Simpson GM, [1999], Antipsychotics in children and adolescents. *J Am Acad Child Adolesc Psychiatry*, 38:537-545

Carter AS, Volkmar FR, Sparrow SS, Wang JJ, Lord C, Dawson G, Fombonne E, Loveland K, Mesibov G, Schopler E [1998], The Vineland Adaptive Behavior Scales: supplementary norms for individuals with autism. *J Autism Dev Disord* 28:287-302

CDC: National Center for Health Statistics [2000], Body mass index-for-age percentiles: Boys, 2 to 20 years; Girls, 2 to 20 years [CDC Web Site]. Available at http://www.cdc.gov/nccdphp/dnpa/bmi/bmi-for-age.htm Accessed August 10, 2004

Cook EH, Leventhal BL (1995), Autistic disorder and other pervasive developmental disorders. *Child Adolesc Psychiatric Clin North Am* 4:381-399

Floris M, Lejeune J, Deberdt W (2001), Effect of amantadine on weight gain during olanzapine treatment. *Eur Neuropsychopharmacol* 1:144-145

Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado PL, Heninger GR, Charney DS (1989), The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), II: validity. *Arch Gen Psychiatry* 46:1012-1016

Gracious BL, Krysiak TE, and Youngstrom EA (2002), Amantadine treatment of psychotropic-induced weight gain in children and adolescents: case series. *J Child Adolesc Psychopharmacol* 12:249-257

Guy W [1976], *ECDEU Assessment Manual for Psychopharmacology*; *Rev*. Rockville, Maryland: National Institute of Mental Health, US Dept of Health, Education, and Welfare. Publication 76-338

Haupt DW, Newcomer JW [2001], Hyperglycemia and antipsychotic medications. *J Clin Psychiatry* 62 Suppl 27:15-26

Hellings JA, Zarcone JR, Crandall K, Wallace D, Schroeder SR [2001], Weight gain in a controlled study of risperidone in children, adolescents, and adults with mental retardation and autism. *J Child Adolesc Psychopharmacol* 11:229-238

Kemner C, Willemsen-Swinkels SHN, de Jonge M, Tuynman-Qua H, van Engeland H [2002], Open-label study of olanzapine in children with pervasive developmental disorder. *J Clin Psychopharmacol* 22:455-460

Koller E, Malozowski S, Doraiswamy P M [2001], Atypical antipsychotic drugs and hyperglycemia in adolescents. *JAMA* 286:2547-2548

Koro CE, Fedder DO, L'Italien GJ, Weiss S, Magder LS, Kreyenbuhl J, Revicki D, Buchanan RW [2002], An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. *Arch Gen Psychiatry* 59: 1021-1026

Kumra S, Jacobsen LK, Lenane M, Karp BI, Frazier JA, Smith AK, Bedwell J, Lee P, Malanga CJ, Hamburger S, Rapoport JL [1998], Childhood-onset schizophrenia: an open-label study of olanzapine in adolescents. *J Am Acad Child Adolesc Psychiatry* 37:377-385

Lord C, Rutter M, LeCouteur A (1994), Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorder. *J Autism Dev Disord* 24:659-685

Lord C, Cook EH, Leventhal BL, and Amaral DG (2000a), Autism spectrum disorders. *Neuron* 28: 355-363

Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL (2000b), The Autism Diagnostic Observation Schedule-Generic: a standard measure of social and communication deficits associated with autism. *J Autism Dev Disord* 30:205-223

Malone RP, Cater J, Sheikh RM, Choudhury MS, Delaney MA [2001], Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. *J Am Acad Child Adolesc Psychiatry* 40:887-894

Martin A, Scahill L, Anderson GM, Aman M, Arnold LE, McCracken J, McDougle CJ, Tierney E, Chuang S, Vitiello B, Research Units on Pediatric Psychopharmacology Autism Network [2004], Weight and leptin changes among risperidone-treated youths with autism: 6-month prospective data. *Am J Psychiatry* 161:1125-1127

McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, Arnold LE, Lindsay R, Nash P, Hollway J, McDougle CJ, Posey D, Swiezy N, Kohn A, Scahill L, Martin A,

Koenig K, Volkmar F, Carroll D, Lancor A, Tierney E, Ghuman J, Gonzalez NM, Grados M, Vitiello B, Ritz L, Davies M, Robinson J, McMahon D, Research Units on Pediatric Psychopharmacology Autism Network [2002], Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 347: 314-321

McDougle CJ, Holmes JP, Carlson DC, Pelton GH, Cohen DJ, Price LH [1998], A double-blind, placebo-controlled study of risperidone in adults with autistic disorder or other pervasive developmental disorders. *Arch Gen Psychiatry* 55: 633-641

Meyer JM [2001], Novel antipsychotics and severe hyperlipidemia. *J Clin Psychopharmacol* 21:369-174

Potenza MN, Holmes JP, Kanes SJ, McDougle CJ (1999), Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. *J Clinical Psychopharmacol* 19: 37-44

Robertson JM, Tanguay P, L'Ecuyer S, Sims A, Waltrip C (1999), Domains of social communication handicap in autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*, 38:738-745

Sparrow SS, Balla DA, Cicchetti DV [1984], *Vineland Adaptive Behavior Scales*. Circle Pines, M N: American Guidance Service, Inc.

Tanguay PE, Robertson J, Derrick Ann [1998], A dimensional classification of autism spectrum disorder by social communication domains. *J Am Acad Child Adolesc Psychiatry*, 37:271-277

Tanguay PE (2000), Pervasive developmental disorder-a ten-year review. *J Am Acad Child Adolesc Psychiatry* 39:1079-1095

Tollefson GD, Beasley CM Jr, Tamura RN, Tran PV, Potvin JH [1997], Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. *Am J Psychiatry* 154:1248-1254

Turrone P, Kapur S, Seeman MV, Flint AJ [2002], Elevation of prolactin levels by atypical antipsychotics. *Am J Psychiatry* 159:133-135

Volkmar FR (1991), Autism and pervasive developmental disorders. In *Child and Adolescent Psychiatry: A Comprehensive Textbook*, Melvin Lewis, ed. Baltimore: Williams and Wilkins

Volkmar FR, Klin A, Siegel B, Szatmari P, Lord C, Campbell M, Freeman BJ, Cicchetti DV, Rutter M, Kline W, et al. (1994), Field trial for autistic disorder in DSM-IV. *Am. J Psychiatry* 151:1361-1367

Volkmar (2001), Pharmacological interventions in autism: theoretical and practical issues. *J Clin Child Psychol* 30: 80-87

Wirshing DA, Erhart SM, Pierre JM, Boyd JA [2000], Nonextrapyramidal side effects of novel antipsychotics. *Curr Opin Psychiatry* 13:45-50

Wudarsky M, Nicolson R, Hamburger SD, Spechler L, Gochman P, Bedwell J, Lenane MC, Rapoport JL (1999), Elevated prolactin levels in pediatric patients on typical and atypical antipsychotics. *J Child Adolesc Psychopharmacol* 9:239-245

Table 1 Paired t-Test for Pre-Drug Versus Post-Drug ADOS-G Social Communication Domains.

Domain	n	Pre-Drug Mean ±SD	Post-Drug Mean ±SD	Mean Difference ±SD	p-value
Affective Reciprocity	10	2.0 ±0.4	1.3 ±0.7	0.7 ±0.5	0.002
Joint Attention	10	2.0 ±0.3	1.3 ±0.7	0.7 ±0.6	0.003
Theory of Mind	10	2.1 ±0.3	1.5 ±1.2	0.6 ±1.1	0.111
Total Social Communication Score	10	6.1 ±0.7	4.0 ±2.1	2.1 ±1.6	0.003

Table 2 Paired t-Test for Pre-Drug Versus Post-Drug ADOS-G Diagnostic Algorithm Scores.

Algorithm Score	n	Pre-Drug Mean ±SD	Post-Drug Mean ±SD	Mean Difference ±SD	p-value
Communication	10	5.9 ±1.4	4.7 ±2.4	1.2 ±2.4	0.147
Social Relatedness	10	12.8 ±1.2	8.7 ±3.6	4.1 ±3.2	0.003
Communication + Social Relatedness	10	18.7 ±2.3	13.4 ±5.7	5.3 ±5.4	0.013

Table 3 Comparison of Scores for Secondary Outcome Measures before and after Olanzapine Treatment.

Outcome	n	Pre-drug Mean ±SD	Post-drug Mean ±SD	Mean Difference ±SD	p-value
Vineland Socialization	10	39.6 ±21.0	49.1 ±23.1	-9.5 ±4.6	<0.001
Vineland Communication	10	42.3 ±34.0	53.3 ±31.1	-11.0 ±8.6	0.003
Age-Equivalent Vineland Socialization	10	23.5 ±26.5	34.7 ±40.1	-11.2 ±13.9	0.031
Age-Equivalent Vineland Communication	10	37.5 ±62.0	44.0 ±60.2	-6.5 ±6.3	0.010
Vineland Maladaptive Scale Total [Parts I and II]	10	37.3 ±9.2	11.6 ±8.8	25.7 ±11.1	<0.001
ABC-CV Lethargy	10	14.0 ±5.4	4.7 ±3.9	9.3 ±5.2	<0.001
ABC-CV Stereotypies	10	9.8 ±5.6	4.5 ±4.4	5.3 ±3.5	<0.001
ABC-CV Hyperactivity	10	32.3 ±10.9	18.6 ±11.3	13.7 ±6.3	<0.001
ABC-CV Excessive Speech	10	5.2 ±3.4	3.4 ±3.5	1.8 ±2.9	0.085
ABC-CV Irritability	10	22.6 ±8.9	10.8 ±9.5	11.8 ±5.1	<0.001
ABC-CV Total	10	83.9 ±29.9	42.0 ±28.9	41.9 ±18.8	<0.001
CY-BOCS	10	13.4 ±1.8	9.9 ±4.7	3.5 ±3.9	0.021
CGI – Severity	10	4.6 ±0.7	3.8 ±0.6	0.8 ±0.4	<0.001
CGI - Improvement	10	2.6 ±0.5	1.3 ±0.5	1.3 ±0.5	<0.001

Note: Lower scores are better for all of these scales except for the Vineland Communication and Socialization (including age-equivalent) subscales for which a higher score is bet

Table 4 Spearman Correlation between ADOS-G Social Communication Scores and Vineland Socialization Scores.

ADOS-G Domain	Vineland Domain	n	r_s	p-value
Affective Reciprocity (pre-drug)	Vineland Socialization (pre-drug)	10	-0.601	0.066
	Age-Equivalent Vineland Socialization (pre-drug)	10	-0.631	0.051
Affective Reciprocity (post-drug)	Vineland Socialization (post-drug)	10	-0.812	0.004
	Age-Equivalent Vineland (post-drug)	10	-0.812	0.004
Joint Attention (pre-drug)	Vineland Socialization (pre-drug)	10	-0.602	0.066
	Age-Equivalent Vineland Socialization (pre-drug)	10	-0.581	0.078
Joint Attention (post-drug)	Vineland Socialization (post-drug)	10	-0.821	0.004

Age-Equivalent Vineland Socialization (post-drug)	10	-0.821	0.004

Table 4 (continued)

ADOS-G Domain	Vineland Domain	n	r_s	p-value
Total Social Communication (pre-drug)	Vineland Socialization (pre-drug)	10	-0.867	0.001
	Age-Equivalent Vineland Socialization (pre-drug)	10	-0.894	<0.001
Total Social Communication (post-drug)	Vineland Socialization (post-drug)	10	-0.817	0.004
	Age-Equivalent Vineland Socialization (post-drug)	10	-0.817	0.004

Table 5. Spearman Correlation between Change (Pre-Drug Values Subtracted from Post-Drug Values) in ADOS-G Social Communication Scores and Change in Vineland Socialization Scores.

ADOS Domain	Vineland Domain	n	r_s	p-value
Change in Affective Reciprocity	Change in Vineland Socialization	10	-0.667	0.035
	Change in Age-Equivalent Vineland Socialization	10	-0.715	0.020
Change in Joint Attention	Change in Vineland Socialization	10	-0.492	0.148
	Change in Age-Equivalent Vineland Socialization	10	-0.571	0.085
Change in Total Social Communication Score	Change in Vineland Socialization	10	-0.638	0.047
	Change in Age-Equivalent Vineland Socialization	10	-0.762	0.010

Table 6. Spearman Correlation between ADOS-G Algorithmic Scores and the Vineland Counterpart Scales.

ADOS Algorithm Scores	Vineland Domain	n	r_s	p-value
Communication Subscale (pre-drug)	Vineland Communication (pre-drug)	10	0.019	0.959
Communication Subscale (post-drug)	Vineland Communication (post-drug)	10	-0.542	0.106
Social Relatedness Subscale (pre-drug)	Vineland Socialization (pre-drug)	10	-0.303	0.395
Social Relatedness Subscale (post-drug)	Vineland Socialization (post-drug)	10	-0.730	0.017
Communication + Social Relatedness (pre-drug)	Vineland Socialization + Vineland Communication (pre-drug)	10	-0.086	0.813
Communication + Social Relatedness (post-drug)	Vineland Socialization + Vineland Communication (post-drug)	10	-0.677	0.032

Figure 1. Time Trend Analysis of the Vineland Socialization Domain (First Significant Change: Baseline Versus Week 2, p=0.011)

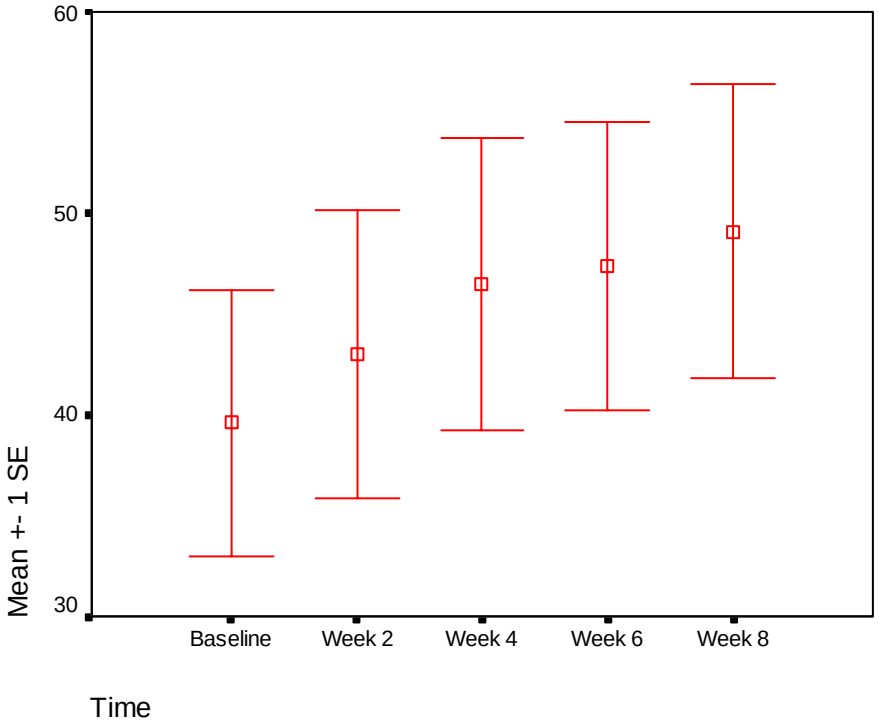

Figure 2. Time Trend Analysis of the Vineland Communication Domain (First Significant Change: Baseline Versus Week 2, p=0.001)

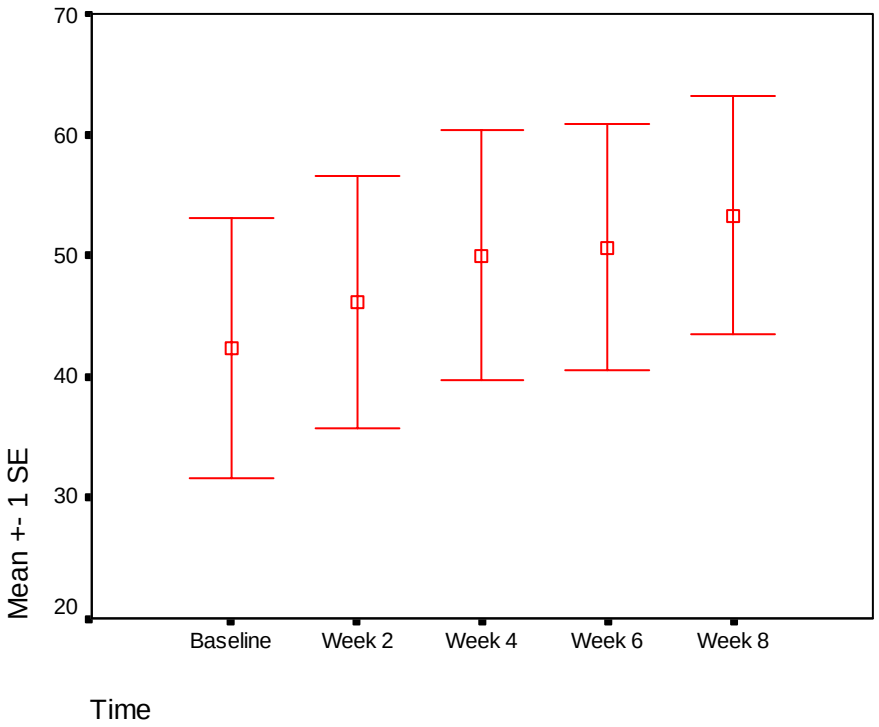

Figure 3. Time Trend Analysis of the Vineland Maladaptive Behavior Scale (First Significant Change: Baseline Versus Week 2, p=0.005)

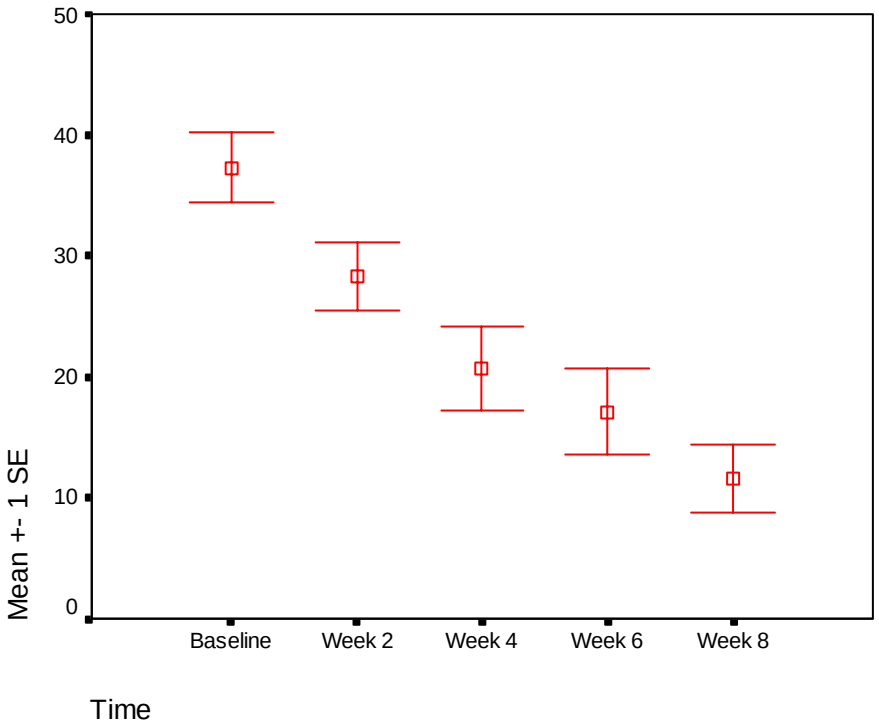

Figure 4. Time Trend Analysis for ABC-CV Total Scores (First Significant Change: Baseline Versus Week 4, p=0.002)

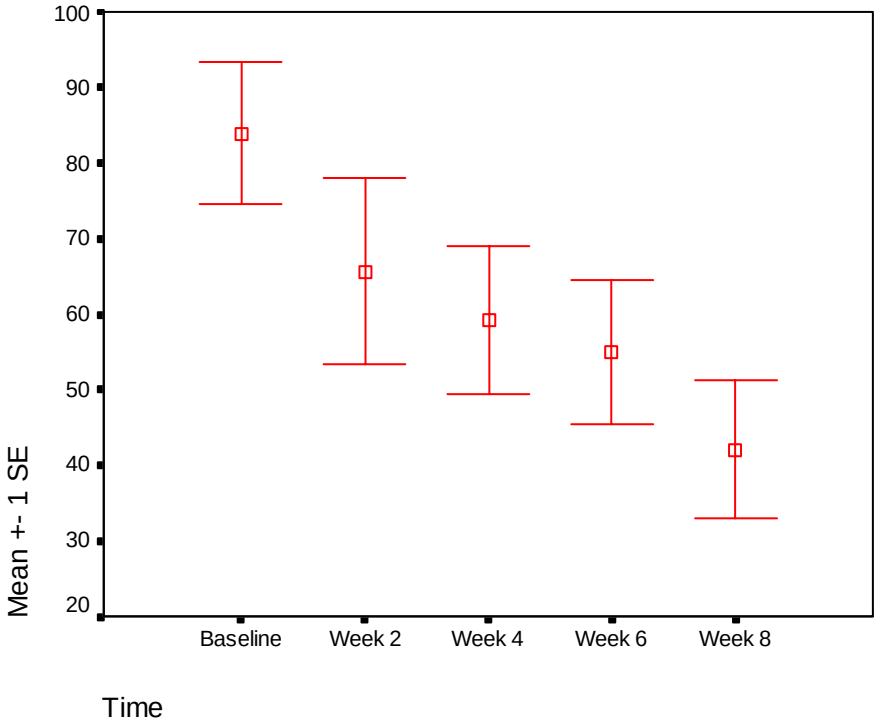

Figure 5. Time Trend Analysis for CGI-Improvement (First Significant Change: Week 2 Versus Week 4, p=0.015)

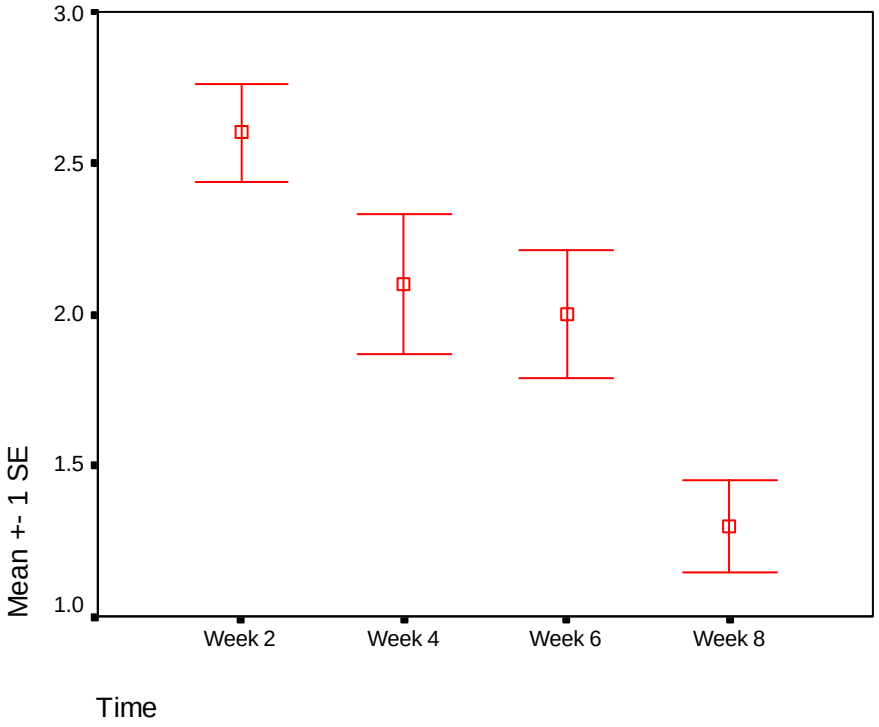

Figure 6. Time Trend Analysis for CGI–Severity (First Significant Change: Baseline Versus Week 6, p=0.001)