Critical Review:
Is a gluten-free/casein-free diet effective in improving language and communication skills in individuals with Autism Spectrum Disorder?

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This critical review examined the effects of a gluten-free/casein-free (GFCF) diet on language and communication skills in individuals with Autism Spectrum Disorder (ASD). All studies included individuals diagnosed with ASD, with abnormal urine peptide levels, and who were between the ages of 2 and 22 years. 3 of the studies were randomized clinical trials, 1 was a single group design, and the last was a systematic review. Outcomes of these studies indicate mixed evidence for improvements in language and communication skills, and should be interpreted with caution due to the inherent limitations in methodology and analysis in many of the studies.

Introduction
ASD is a lifelong condition that can be characterized by deficits in the areas of social interaction, verbal and nonverbal communication, and repetitive behaviors (APA, 2000). With an increasing number of individuals being diagnosed with the disorder (Fombonne, 2003) parents are anxious to find a treatment strategy. Though there is no known cure for ASD, parents have turned to alternative means in an attempt to treat the symptoms. One alternative approach includes the GFCF diet, even though research regarding its effectiveness has thus far been limited. The GFCF diet as an alternative approach in treating ASD has received a significant amount of attention over the years largely due to parent and teacher testimonials, and reports of poorly controlled studies.

Previous research has shown that individuals with ASD often times present with abnormal urinary peptide levels, suggesting insufficient break down of the peptides gluten, gliadin, and casein (Reichelt, 1981; Cade, 2000). Gluten is commonly found in wheat and other cereals and casein in milk and milk products. The question remains whether the removal of gluten and casein from the diet of individuals with ASD would result in improved language and communication skills, as previous studies have suggested might be the case (Knivsberg, 1999; Knivsberg, 2003; Whiteley, 1999; Cade, 2000).

Objectives
The primary purpose of this paper is to provide a critical review of the literature, examining the effects of a GFCF diet on language and communication skills in individuals diagnosed with ASD. A secondary purpose is to discuss the clinical implications of these findings and to make suggestions regarding future research in the area.

Methods
Search Strategy
Computerized databases including PubMed, CINAHL, PsycINFO, and Scopus were searched. The literary search was limited to English journal articles and reviews, with no limit in terms of year of publication. Search terms included : (Autism) AND (gluten-free/casein free diet) AND (communication) OR (language)).

Selection Criteria
Studies selected included a minimum of 1 group, where the intervention being provided removed both gluten and casein from the diet of individuals diagnosed with ASD. As well, language or communication had to be the outcome of interest. No limits were set on participant’s demographics (e.g., age, race, gender, socio-economic status).

Data Collection
Results of the literature review yielded 5 articles consistent with the selection criteria, 3 randomized clinical trials, 1 single group design, and 1 systematic review. The intent of this review was to focus on the effect of a GFCF diet on language and communication skills in individuals with ASD.

Results
RANDOMIZED CLINICAL TRIALS
Elder et al. (2006) conducted a randomized, double blind, repeated measures, crossover design in which they tested the efficacy of a GFCF diet in treating severity of autistic symptoms as measured by the CARS (Childhood Autism Rating Scale), the ECOS (Ecological Communication Orientation Scale), and...
direct behavioral observation. Child behaviors included initiating, responding, and intelligible words spoken. Also coded were parent initiating, responding, and expectant waiting. Data were collected at 3 points; immediately before the diet, at the end of the first dietary condition (week 6), and at completion (week 12). Another goal of the study was to evaluate the role of parent behavior and placebo effects of a GFCF diet. Participants included 13 children diagnosed with ASD, aged 2-16 years, who were chosen by purposive sampling from the Centre for Autism and Related Disabilities and/or Child Psychiatry Services. Inclusion was based on a diagnosis of ASD according to DSM IV criteria, and a score above cut-off on each symptom domain of the Autism Diagnostic Interview Revised (ADI-R). Children were excluded from the study if their medical histories and/or physical examination indicated physical or sensory-impairment or significant medical problems. Participants were provided all meals and snacks, and parents were given a list of allowed foods in case of emergencies, and were asked to record their child’s diet intake in order to monitor compliance. Nutritional adequacy was monitored, and if necessary a vitamin and/or mineral supplement was provided. For each treatment comparison, a two-sided, two sample T-test was utilized as to not ignore order.

Group data indicated no statistically significant difference between groups with the CARS, ECOS, behavioral frequencies or observed parent behaviors, even though several parents reported improvements in their children.

LIMITATIONS/LEVEL OF EVIDENCE
Statistically non-significant findings could be the effect of a small sample size, and/or large within-group variance, potentially leading to a type 2 error. The study sample was heterogeneous in terms of age, severity of autism, and cognitive abilities, which would make it difficult to draw meaningful conclusions about the group as a whole. Though most parents were diligent concerning dietary restrictions, there were several reports of children sneaking food from classmates or siblings, which could have had a negative result on diet intervention outcomes. Non-significant findings could also be due to a relatively short diet period. Authors discovered that while the CARS was a useful screening tool, it may not have detected some of the more subtle changes reported by families. Also, there is some speculation regarding parental placebo effects related to the GFCF diet effectiveness, which may account for families reporting improvements that were not empirically supported by the study. For the most part, authors were able to produce and implement a GFCF placebo diet, considering 8 of the parents were unable to correctly distinguish between placebo and experimental diets.

Participant selection and identification was appropriate (purposive sampling, scores above cut-off on the ADR-I), however it was heterogeneous in multiple respects, and could have benefited from more purposeful matching. Instruments and procedures utilized for measuring dependant variables were also appropriate given the use of gold standard rating scales as well as multiple diagnostic assessment tools. Given the rigorous methodological study design and the use of double blinding, this Level I study did not provide compelling evidence for the use of a GFCF diet in terms of improving language and communication skills, and should weigh highly on the final decision to suggest this alternative mean.

Seung et al. (2007) retrospectively examined the effects of a GFCF diet in improving verbal/nonverbal communication in children with ASD. This study was completed as a follow-up to the Elder et al. (2006) study, utilizing existing videotapes of parent and child interactions. Children whose medical history or physical exam indicated sensory, physical, or significant medical problems were excluded, however 38% of participants were on prescription anticonvulsant, antipsychotic, or antihypertension medications. A certified nutritionist prepared the food for the 12 week study period, and parents and children were told to continue on with their daily routines. 15 minute video recordings of at-home parent-child play were analyzed. Recordings were made at baseline, after 6 weeks on one diet, and then after 6 weeks on the alternate diet (GFCF diet vs. No diet). Dependant variables for verbal communication were frequency counts for number of verbal responses to questions, verbal imitations, different words produced and total utterances. All of the participants continued to receive speech-language and occupational therapy while they were enrolled in the study, and parents were asked to not add or increase the frequencies of other therapies and interventions during the study to limit potential confounds. Specifically, the main research questions for this study were: Are there differences in the number of verbal social exchanges and the number of lexical productions between the 2 diet conditions? Data for the children’s verbal communication behaviors were analyzed using nonparametric (Friedman) tests for repeated measures. Additional analyses for each variable were performed using a subset of data for the 7 specific children whose
parents had previously reported perceiving positive gains in language since enrolled in the Elder et al. study.

Authors found no statistically significant differences in verbal and non-verbal communication outcomes between the GFCF and regular diet conditions. This is contrary to feedback from the 7 parents in the Elder et al. study.

LIMITATIONS/ LEVEL OF EVIDENCE
Limitations include; a small number of participants with large variability on the obtained measures, and the fact that the study was a secondary analysis using existing data. The diet period was also relatively short. This study also raises questions regarding the validity of parental reports. Because the majority of children in the study used predominantly single-word utterances, the measure of verbal imitation might not be the most sensitive measure of verbal communication. Other possible limitations of the study include the lack of monitoring to ensure children were not sneaking food outside of the food being provided (e.g., from siblings, school mates, etc), and possible confounding variables such as prescription anticonvulsants, antipsychotics, and antihypertension medications, as well as other therapies (e.g., SLP, OT, etc).

Results of this Level 1 study demonstrate that double-blind clinical trials of diet interventions are feasible, but do not support the efficacy of the GFCF diet as a means of improving verbal communication in children with ASD, at least for a dietary intervention lasting 6 weeks. Instruments and procedures utilized to analyze pre-existing video tapes are inherent to limitations though a reliability agreement of 96% was obtained between transcribers.

Knivsberg et al. (2003) conducted a randomized, single blind, controlled design which evaluated the effect of a GFCF diet in children with ASD. Participants included 20 children matched pair-wise according to age, cognitive level, and severity of autistic behaviors. Participants were aged 2-16 years. This study relied on an observation scheme to assess children’s autistic behaviors (DIPAB- Diagnosis of Psychotic Behavior in Children), as well as parent reports. Behaviors being monitored included communicative aspects, reciprocal social interactions, emotions, learning, play behavior, and movements. Non-verbal cognitive levels were measured with the Leiter International Performance Scale. The experimental period was 1 year; and children were tested at baseline and then re-assessed at 1 year post. Authors hypothesized that they would register a decrease of autistic traits in the diet group but not in the control group. Both repeated measures within the 2 groups of children and between the 2 groups were compared. Nonparametric tests were used for the mixed factorial experiment, and the two-tailed Wilcoxon test for related samples was used to compare the development within the 2 groups. The two-tailed Mann Whitney U test for unrelated samples was used to compare the development between the 2 groups. Mann Whitney U test was chosen because the children in the 2 groups, although pair-wise matched, might differ from each other on other measures and influence.

A significant reduction of autistic behaviors was registered for participants in the diet group, but not for those in the control group (resistance to communication and interaction, reduction of social isolation and strange behaviour) after the dietary intervention. In the control group the picture was somewhat different, 5 remaining children had increased autistic behaviours after the experimental period. Statistical significance of the changes regarding questions related to autistic behaviours were calculated; the means of all the questions decreased for the diet group, and significant changes were found for 12 of 17 questions after the experimental period (verbal communication, reaction when spoken to, etc). Between the 2 groups, significant differences were found for verbal communication, reaction when spoken to, peer relationships, abnormal anxiety, and reactions to changes in environment or routines. A significant increase was found for the diet group on the cognitive test, and a significant decrease was found for the control group. Linguistic age increased in both groups, the diet group had a mean increase of 12 months, and the control group had a mean increase of 9 months.

LIMITATIONS/ LEVEL OF EVIDENCE
This is one of the first known studies with an experimental period lasting 1 year. Though the project leader did not know to which group each child was assigned, placebo effect must be considered. Assumptions that the diet could have a positive effect might have altered the attitude of parents/teachers towards their children, which has proven to be an issue in other studies of the same nature (Seung, 2007; Elder, 2006). Another limitation is that monitoring of compliance was not carried out. A number of variables could have also influenced test results (e.g., mood, illness, etc).

Despite the potential confounding variables which must be taken into consideration when interpreting
the results of this study, this Level 1 experimental design does provide some compelling evidence for the use of a GFCF diet in terms of improving language and communication skills in individuals with ASD, especially considering the relatively long intervention period.

**SINGLE GROUP DESIGN**

Knivsberg et al. (1990; 1995) conducted a single group design with 15 children ranging in age from 6 to 22 years, in which urinary patterns were used to determine which diet should be followed (strictly gluten-free and milk-reduced food/ strictly milk-free and/or gluten-reduced food or a both gluten and milk free diet). Educational and psychological tests were not blind due to parent refusal. All patients were or had been students at Madlavoll School, and conformed to either the diagnosis of infantile autism or childhood onset pervasive developmental disorder. The following tests were run over the 1 year study period; the DIPAB, the C-Raven progressive matrices, the Illinois test of psycholinguistic ability, and the Tafjord observation score for play and activity. Because authors did not know if the various measures were parametrically distributed in the small number of cases studied, Wilcoxon’s paired ranking was used. For correlation calculations, Spearman’s rank-order correlation coefficient was used.

The DIPAB rating of bizarre behaviour revealed that before the diet 9 of 14 children scored in the psychotic group, and after the diet, all changed toward the normal spectrum (though 5 were still showing bizarre behaviour). Results from the C-Raven indicated that the 1 patient who broke the diet had regressed, and the other children changed significantly in their scores (all increasing). An especially large increase in integrated functioning was evident. The Illinois test of psycholinguistics revealed statistically significant changes over that expected for children over a 1 year period. Verbal expression showed the most frequent change while auditory sequential memory showed the least. The Tafjord test of play and activity revealed highly statistically significant changes in the positive direction. Changes in the C-Raven’s progressive matrices were the most profound with an overall improvement of 130 % from initial values over 1 year. Social interaction increased by 22.6 %, structural ability by 16 %, language by 12.2 % and sensory motor by 9 %.

Further retesting was made 4 years after the dietary intervention as a follow-up to the original study, with the same 15 subjects. Positive developments in normalization of urine peptide levels, as well as decreases in odd behaviour and improvements in the use of social, cognitive and communication skills continued but at a much lower rate.

**LIMITATIONS/ LEVEL OF EVIDENCE**

Limitations to the study include; lack of a control group which results in the possibility that changes could be due to extraneous factors (e.g., maturation, placebo effect, other therapies being followed, etc). The authors do not think these long term changes could be due to placebo or maturation alone, because large improvements are typically uncommon in this population. Unfortunately, the data still remains vulnerable to bias due to hopeful expectation. Other limitations include a small and heterogeneous group with no standardized diagnostic assessment which makes it difficult to generalize findings. A final limitation of the study includes the fact that 3 different diet interventions were utilized and outcomes were not reported separately further complicating the analysis of results.

Given the nature of this Level 3 study and the inherent limitations previously described, results should be interpreted with caution and are not hugely compelling in terms of supporting the hypothesis that the use of a GFCF diet is effective in improving language and communication skills in individuals diagnosed with ASD.

**SYSTEMATIC REVIEW**

Mulloy et al. (2009) systematically reviewed the current body of research concerning the effects of a GFCF diet in the treatment of ASD. Inclusion criteria was as follows; the study had to contain at least 1 person with ASD, including Autism, Asperger Syndrome, or PDD-NOS, the intervention being investigated had to involve a diet that removed or reduced the consumption of gluten and/or casein, and finally the dependant variable had to be in some way related to the amelioration of ASD symptoms. Inclusion criteria yielded 15 different studies which were then systematically reviewed twice by two of the authors to ensure analysis was accurate.

Overall, the results of this Level 1 current body of research do not support the use of any type of GFCF diet in the treatment of ASD.

Research studies discussed in this article were appropriate and relevant, and search terms that were utilized were provided. The authors provided clear guidelines for articles that were both included/ excluded, and whenever discrepancies were present (e.g., studies that fit only some of the inclusion criteria), authors provided the reader with their
rationalization for including/excluding the study. Inclusion criteria could have been a little more stringent as it included studies in which the treatment regime consisted not only of removal of gluten and casein from the diet, but other vitamins and allergens, as well as studies in which the diet intervention was only prescribed for a couple of days. Studies examined were discussed in a sufficient amount of detail (participants, specifics of the intervention, dependant variables, results, and certainty of evidence) considering the number of studies being analyzed. The reliability and validity of each study was evaluated in terms of certainty (suggestive, preponderant or conclusive). A discussion of results from study to study is present and a clinical bottom line was stated. Authors also attempted to account for other possible extraneous factors that could affect the results of each study, and also provided guidelines for future recommendations.

This article is valuable because it maintains and strengthens the rationalization for more research to be conducted in the area of GFCF diets in the treatment of ASD symptoms. This systematic review also considers the potential negative effects of following a GFCF diet (e.g., stigmatization, reduced bone cortical thickness, and diversion of other treatment strategies) which is oftentimes omitted in other studies.

**Discussion/Conclusion**

As most studies were similar in design, some general statements can be made regarding limitations and potential confounds. Firstly, all studies consisted of relatively small sample sizes, potentially leading to a type 2 error, as well as heterogeneous groups, which make it difficult to generalize findings. Secondly, with the exception of some studies (Knivsberg 1990; 1995; 2003), the diet intervention periods were relatively short, leading to the possibility that potential benefits may not have been evident until a longer period of time (wash out effect). Other commonly occurring limitations/confounds included: lack of monitoring regarding diet compliance, parental/teacher placebo effects due to unblinding, maturational effects, use of alternative therapies, as well as the use of other prescription medications or vitamin replacements.

Despite the fact that this literature review yielded mixed results concerning the efficacy of a GFCF diet in improving language and communication skills, all studies have something to offer when deciding whether this alternative is a worthwhile avenue to consider. None of the studies are of very weak quality (ranging from Levels 1-3), representing near or gold standard levels of evidence. Elder et al. (2006), Seung et al. (2007), and Mulloy et al. (2009) found no significant evidence for the use of a GFCF diet in terms of language and communication. Given the results of these Level 1 studies, and the aforementioned inherent limitations in methodology of the lower level studies, one cannot say with certainty that a GFCF diet will effect changes in language and communication, particularly in individuals with ASD. Caution should be taken when interpreting the results of lower level studies (Knivsberg et al., 1990; 1995). With that being said however, there does appear to be some evidence to the hypothesis (Knivsberg, 2005), therefore further studies are needed to improve our understanding of what exactly this may be.

**Recommendations**

- Further double-blind studies are needed to rule out placebo effects
- Determine whether one subgroup of ASD may respond better than others to this treatment regime through thorough diagnosing utilizing well established measures
- Include larger numbers of participants to rule out possibility of type 2 errors
- Extend data collection to longer periods of time to account for wash out periods

**Clinical Implications**

Given that some of the studies have shown positive results in terms of language and communication, even for small groups of individuals, it may be worthwhile for some to trial the GFCF diet given the relatively minimal risk of harm, providing proper nutritional guidance is followed, and providing it does not deter parents from seeking other treatment resources. This is especially true for families who are willing or even desperate to try any alternative means in an attempt to treat the symptoms of this complex disorder. For some individuals the use of a GFCF diet might just be beneficial in treating the gastrointestinal issues that some may be experiencing, thus leaving them more open and willing to learn (Mulloy, 2010). Well conducted and adequately powered gold standard trials continue to be needed in this area to rule out other potential explanations. Results from these studies will better equip clinicians and researchers with the answers that parents are so hopeful to find.
References


