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Relationship of Specialty Diets to the Severity of Symptoms Associated with Autism

Rachele Lee

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by

Rachele Lee

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This independent study, submitted by Rachele Lee in partial fulfillment of the requirements for the Degree of Master of Science from the University of North Dakota, has been read by the faculty advisor under whom the work has been done and is hereby approved.

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Faculty Advisor

PERMISSION

Title Relationship of Specialty Diets to the Severity of Symptoms Associated with Autism

Department Nursing

Degree Master of Science

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Abstract

Problem – Autism is a complex umbrella disorder given to children or adults who experience a variety of similar symptoms, yet no concrete cause has been identified for those with the diagnosis. Treatment options are expensive and complex, and no single method has been proven effective for every child with autism. Some parents have utilized dietary intervention but existing evidence on its effectiveness isn't widely studied or recommended by practitioners.

Procedure – A literature review was conducted to determine the current evidence behind the implementation of a gluten-free casein-free (GFCF) diet and its effectiveness on the severity of symptoms associated with an autism diagnosis.

Results – Findings are not 100% consistent with a positive outcome of GFCF dietary implementation in children with autism, yet 11 of the 15 studies examined did show improvements in a variety of behaviors or physiologic processes.

Nursing Implications – Dissemination of findings to local pediatric practice offices and agencies would prove beneficial with the encouragement of recommending a GFCF dietary trial for children diagnosed with autism.

Introduction

It is currently estimated by the Centers for Disease Control and Prevention (CDC) that one in 68 children are diagnosed with an autism spectrum disorder (ASD) (2016). Other sources estimate this number to be even higher, at one in 50 children diagnosed (National Vaccine Information Center, 2013). The autism prevalence rate among girls is approximately 1 in 189 and unfortunately 5 times more likely in boys with a rate of 1 in 42 (CDC, 2016). Although this number continues to increase, there is little known about the true etiologies or cures for the disorder (Elder, 2008).

The CDC (2016) defines ASDs as "a group of developmental disabilities that can cause significant social, communication, and behavioral challenges." Elder (2008) adds that children living with an ASD diagnosis can present with repetitive behaviors and "processing delays that can cause difficulties in responding to others, motor planning, and visual processing" (p. 584). Genius and Bouchard (2010) also note significant symptoms to include "significant aggression, tendencies toward self-injury and self-harm, irritability, as well as hyperactive and erratic behavior" (p. 114).

The exact cause of ASD is unknown but there is belief that a genetic susceptibility to environmental factors could play a major role. It is also hypothesized that immunologic and gastrointestinal permeability play a role in the neurologic and behavioral symptoms associated with autism (Mulloy et al, 2010). Many children with ASD will experience some form of chronic constipation or diarrhea, suggestive of gastrointestinal disorder. Although there has not been a proven cure, many studies are stating that removing both gluten and casein (a protein found in cow's milk) from the diet of children with autism can lead to a decrease in the severity of symptoms associated with the disorder (Knivsberg, Reichelt, Hoien, & Nodland, 2002).

Purpose

Many children with autism will endure years and years of traditional therapy in attempts to improve "typical" behavior and reduce symptoms related to their diagnosis (Hsu, Lin, Chen, Wang, & Wong, 2009). The average cost of treatment for many individuals on the spectrum is an outstanding $60,000-$70,000 PER YEAR for various therapies, schooling, and alternative treatment options (Parker-Pope, 2010). Treatment recommendations generally include educational intervention, physical and developmental therapy, and behavioral treatment (Elder, 2008). Yet "there is increasing recognition that the expression of ASD in some sub-groups may

also include a number of additional elements beyond psychiatry that may be potentially relevant" (Whiteley et al, 2010, p.88). Diet changes are under scrutiny as a physical trigger for psychological symptoms. It is possible that dietary change can have a great impact on behavior and therefore lessen the amount of therapy or other treatments necessary, yet this form of alternative type therapy is not widely studied or utilized within the autism community.

Significance

Autism rates are soaring among children with a current estimate that one in every 50-68 children is diagnosed with an ASD. This is a 72% increase from 2007 when estimates were one in every 88 children diagnosed (National Vaccine Information Center, 2013). "For some time clinical experience has supported the existence of a functional relationship between the central nervous system (CNS) and the gastrointestinal (GI) tract, a paradigm known as the 'brain-gut axis'" (Julio-Pieper, Bravo, Aliaga, & Gotteland, 2014, p. 1188). "The first ever formal description of autistic symptoms contains reference to GI symptoms and dietary issues being present in some cases" (Whiteley et al, 2013, p. 2).

The intestinal mucosa is the largest surface of interaction between internal body systems and the external environment. It's dual functions include regulation of the absorption of water, electrolytes, and nutrients from the intestines into circulation, while at the same time preventing the penetration of harmful pathogens and toxins, including dietary antigens (Julio-Pieper et al, 2014). The theory behind the removal of gluten and casein of a child with autism's diet involves the belief that children with autism cannot break down the gluten and casein proteins completely or appropriately. This inappropriate breakdown results in opioid peptides that are able to leak through the intestinal wall (leaky gut syndrome), enter the bloodstream, cross the blood-brain barrier, and ultimately affect neurotransmission within the central nervous system (Elder, 2008).

Studies have shown that many children with autism suffer from gastrointestinal inflammation due to the ingestion of these proteins, which eventually leads to the leaky gut syndrome that allows the peptides to enter the bloodstream (Knivsberg et al, 2002).

The impaired neurotransmission in children with autism, as a result of ingesting gluten and/or casein products, is believed to attribute to difficulties in communication and use of language, affect attention and concentration, impair social integration and interaction, contribute to altered pain perception and lead to self-injurious behaviors, contribute to stereotypical or repetitive behaviors, impair motor coordination, and contribute to hyperactivity (Whiteley et al., 2013). Therefore, it is possible that removing these proteins from the diet of a child with autism could lead to an improvement or elimination of some or all of his or her symptoms.

Theoretical Framework

The framework for this study is based upon a physiological theory known as the leaky gut hypothesis, which correlates poor gut health and function to neurological symptoms specifically in children with an ASD (Lang, Hauser, & Reissmann, 2015). Oftentimes, children with autism will exhibit a variety of gastrointestinal disturbances. These may include one or all of the following: constipation, diarrhea, abdominal pain and/or abdominal bloating. Some parents' even report that these symptoms began around the same time their child regressed and began experiencing autism symptoms (White, 2003).

The "GI tract works very closely with the immune system to maintain homeostasis and protects our body against microorganisms and foreign antigens" (Samsam, Ahangari, & Naser, 2014, p. 9944). The intestinal lumen is lined by only a single layer of epithelial cells, which are responsible for preventing various intestinal contents from escaping the gut and entering the bloodstream. These epithelial cells are joined together by filaments forming tightly bound

intercellular junctions on their lateral walls (Liu, Li, & Neu, 2005). “The idea that the integrity of the intestinal mucosal lining, referred to as the intestinal mucosal barrier, is compromised in autism is embodied in the ‘leaky gut hypothesis.’ According to this hypothesis, the intestinal mucosa is abnormally permeable in autism” (White, 2003, p. 642). In other words, the junctions between the epithelial cells are compromised and are unable to properly regulate what may enter and escape the intestinal lumen.

The exact cause of this intestinal dysfunction isn’t clearly known but speculations have been made on a few different causes. One possible cause of intestinal inflammation and dysfunction seen in children with autism, and the primary focus of this project, is due to antigens in the diet. Gliadin is the peptide that is derived from gluten and is believed to cause or contribute to increased intestinal permeability the same way it affects those with Celiac Disease. Similarly, “children with cow’s milk allergy also exhibit inflammation of the intestinal lamina propria and partial villous atrophy after ingesting milk; inflammation is reversed when milk is excluded from the diet. Hence, milk proteins may also cause changes in gut permeability” (White, 2003, p. 643).

According to the leaky gut hypothesis, “it is proposed that gliadomorphins and casomorphins arising from the partial luminal digestion of dietary gliadin and casein, respectively, are absorbed through a leaky gut, enter into the CNS, and interfere with normal brain function because their functional properties mimic the opioid hormone beta-endorphin” (White, 2003, p. 646). Petra et al (2015, p. 985) also support this idea stating, “Neuro/immune-active substances derived from the intestinal lumen can penetrate the gut mucosa, be transported by blood, cross the blood–brain barrier (BBB), and affect the CNS.”

"GI abnormalities are often seen to correlate with the severity of the ASD behavioral problems and current literature favors a gut-brain interaction where GI abnormalities may be involved in the pathogenesis or severity of ASD" (Samsam et al, 2014, p. 9944). Due to this hypothesis, a diet free from the gluten and casein proteins is recommended to alleviate GI as well as neurologic or behavioral symptoms.

Definitions

Autism Spectrum Disorder (ASD) – "Autism spectrum disorder (ASD) and autism are both general terms for a group of complex disorders of brain development. These disorders are characterized, in varying degrees, by difficulties in social interaction, verbal and nonverbal communication and repetitive behaviors" (Autism Speaks, 2016).

Casein – a phosphoprotein of mammal milk (Merriam-Webster, 2015).

Celiac Disease – "an autoimmune disorder that can occur in genetically predisposed people where the ingestion of gluten leads to damage in the small intestine" (Celiac Disease Foundation, 2016).

Gluten – "a tenacious elastic protein substance especially of wheat flour that gives cohesiveness to dough" (Merriam-Webster, 2015).

Lamina Propria – "a highly vascular layer of connective tissue under the basement membrane lining a layer of epithelium" (Merriam-Webster, n.d.).

Leaky-Gut Syndrome – Impaired intestinal permeability leading to abnormal intestinal absorption (Pusponegoro, Ismael, Firmansyah, Sastroasmoro, & Vandenplas, 2015).

Opioid – "Any of a group of endogenous neural polypeptides (as an endorphin or enkephalin) that bind especially to opiate receptors and mimic some of the pharmacological properties of opiates —called also opioid peptide" (Merriam-Webster, 2015).

Peptide – "Any of various amides that are derived from two or more amino acids by combination of the amino group of one acid with the carboxyl group of another and are usually obtained by partial hydrolysis of proteins" (Merriam-Webster, 2015).

Process

The University of North Dakota's Harley E. French Library of the Health Sciences was used to conduct a search of related literature. The CINAHL database was the initial database used when performing the search. According to the EBSCOhost website, CINAHL provides "hundreds of nursing and allied health journals" with "records dating back to 1937" (EBSCO Industries, 2013). PubMed was used as a secondary source of information. "PubMed is a free resource that is developed and maintained by the National Center for Biotechnology Information (NCBI), at the U.S. National Library of Medicine (NLM), located at the National Institutes of Health (NIH)" (NCBI, 2005).

When conducting the search in the CINAHL database the terms "autism" AND "gluten" AND "casein" were entered with the "find all my search terms" used as the search mode. This yielded 22 results found with publication dating back to the year 2000. After a brief overview, eight articles were reviewed in more detail and only two articles were found to be relevant to the project topic. A second search term was performed with the terms "gfcf autism." This search revealed five results, four of which were included in the original search. The fifth article was reviewed in detail and determined to be pertinent to the project topic.

Another search was conducted through the PubMed database with the search term "gfcf autism" which yielded six results. Three articles were reviewed in detail and it was determined that only one was relevant. Subsequently the terms "autism and gluten and casein" were entered into the search field. This search yielded 53 results, seven of which were reviewed in detail and

three additional were determined to be relevant. A third search was entered into the PubMed database with the search term “gluten autism” which yielded 115 results. Thirteen articles were reviewed in detail and it was determined that eight articles were relevant, which concluded the search.

Article reference sections for both database searches were reviewed prior to making the final determination of relevant articles. It was found that references that appeared relevant had already been included in the original search results; therefore additional sources from references were not utilized.

Review of the Literature

Specific studies regarding the elimination of gluten and casein from an autistic child’s diet are limited and many are now outdated. Fifteen studies were examined in detail with varying results. Many different symptoms were measured and varied from study to study. Some of these included communication, social isolation, eye contact, mutism, learning skills, hyperactivity, stereotypical activity, hygiene, panic attacks, self mutilation, gastrointestinal problems, social interaction, imagination, tantrums, anxiety, seizure activity, inattention, aloofness, need for routine, peer relationships, empathy, physical contact, language peculiarities, peculiar interests, sensory symptoms, and motor skills.

Four of the studies examined were case reports on a single child ranging in ages from three, to 23 years old and detailed his or her history and symptom improvement or resolution following a gluten-free or gluten and casein-free diet (Hsu, Lin, Chen, Wang, & Wong, 2009; Genius & Lobo, 2014; Herbert & Buckley, 2013; Genius & Bouchard, 2010). All four of the children described in these articles experienced positive improvements in autistic behaviors or complete resolution of symptoms leading to a complete recovery.

Hsu et al (2009) followed one child aged 42 months at the initiation of the study who was diagnosed with autism, growth and developmental retardation, and CHARGE (Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness) syndrome. The child was observed over an 11-month time span and data was collected throughout that time frame. Improvements in all areas of development were noted at the 11-month mark of follow-up. Weight percentiles were also measured, which were originally below the third percentile and had increased to approximately the 15th percentile by that time. Strengths of this article included the fact that objective developmental measurement tools were utilized before and after dietary intervention and included intermittent follow-up periods. Also, the length of time for follow up was significant, allowing for complete healing of the gastrointestinal system if gluten and/or casein proved a causative factor. Limitations included the fact that this was just a single observed case report and double blind observations before and after initiation of diet were not performed. Also, the child continued to receive physical, occupational, speech, and sensory integration therapies throughout dietary intervention, which could also have an effect on the final outcome.

Genius and Lobo (2014) reported on a now 23-year-old female with a longstanding history of auditory and visual hallucinations, along with gastrointestinal disturbances, which all began around the age of four or five. The subject experienced extreme auditory and visual hallucinations throughout her entire life as well as being diagnosed with irritable bowel syndrome. Her parents never sought medical treatment or medication for her symptoms but she did participate in some religious counseling. By the time she entered college and after other unsuccessful dietary elimination trials, she decided to independently eliminate gluten from her diet. This resulted in complete resolution of her symptoms. Hallucinations would return within

hours of any slight accidental gluten exposure and last 24-72hrs, giving her a clear indication of a definitive correlation between gluten ingestion and her neurologic symptoms. Strengths of this article included the fact that symptoms completely resolved after gluten elimination without any other intervention, providing a clear correlation. Also this subject was not diagnosed with autistic disorder or any other learning disability and was able to give an accurate description and detail of her symptoms. Limitations included the fact that there wasn't any concrete laboratory data utilized as subject refused, given that her symptoms completely resolved and she didn't find it necessary. It was not mentioned whether physician monitoring was present.

Herbert & Buckley (2013) described a young girl, now aged 13, who had been developing typically up until the age of four when she went into her pediatrician's office for a well-child checkup. The article states that after that visit the girl unfortunately experienced severe, regressive autism and reverted back to an 18-month level of language and development. Her parents had attempted various treatment options with very limited success before starting her on a GFCF diet. After diet implementation she had showed a significant improvement in autistic behaviors. Over a period of several years her Childhood Autism Rating Score (CARS) decreased from an initial score of 49, representing severe autism, down to a score of 17, which represents non-autistic behaviors. During puberty the girl also began to experience seizure activity, which her parents negated with a GFCF ketogenic diet. Both dietary interventions provide evidence and hope that there is a possible correlation between diet and neurologic symptoms. Strengths of this article included the fact that symptoms and interventions are detailed chronologically providing a clear understanding of the sequence of events. Also an EEG was performed pre and post ketogenic dietary intervention to show concrete evidence of diminished seizure activity with no other changes in treatment plan. Limitations included the fact that the cause of significant

regression into autism in a previously neurotypical 4-year-old is not mentioned. Also, other biomedical treatments and supplements were being utilized and changed throughout her years of treatment. Lastly, the source of information was not mentioned.

Genius and Bouchard (2010) provided a description of a 5-year-old boy who was diagnosed with severe autism at the age of three, who also experienced multiple abnormal GI symptoms. Through laboratory testing the child was eventually diagnosed with Celiac Disease. A gluten-free diet was implemented along with dietary and supplemental measures. After just 3 short months, the child could be mainstreamed back into a regular education classroom without any individualized special education plan and his autism symptoms completely disappeared. Strengths of this article included the fact that concrete laboratory data was utilized to make a formal diagnosis of Celiac Disease. Limitations would be that follow up biochemical nutritional testing was declined by his parents due to a complete resolution of symptoms and the source of information is unknown.

Two cohort studies were reviewed (Pennesi & Klein, 2012; Cade, Privette, Fregly, Rowland, Sun, Zele, Wagemaker, & Edelstein, 2000) which also showed improvements in autistic behavior and laboratory values after implementation of a GFCF diet.

Pennesi & Klein (2012) conducted a survey for the parents of 387 children diagnosed with an ASD who were already following a GFCF diet to some degree. The study aimed to evaluate whether the implementation of a GFCF diet resulted in improvements in autistic behaviors, social behaviors, and GI symptoms. A 90 item online questionnaire was administered to each of the 387 parent participants. Diet implementation, compliance, and length of implementation were measured. Also included were parental reports of observable changes in their child's behaviors as well as GI symptoms. Results show that implementing a GFCF diet

may positively impact autistic behaviors and GI symptoms, specifically for those with previous GI symptoms and food allergies reported ($p<0.05$). Strict adherence seems to have a better outcome than those who have dietary errors even just on occasion. Strengths of this study included the fact that explanation of the purpose was clear, there was a large sample size, and participants were grouped by specific diagnosis as well as diet adherence. Limitations included the fact that there weren't any exclusion criteria for participants and there weren't any control methods regarding diet implementation. Also the survey was subjective and responses could vary a great deal with each participant.

Cade et al (2000) also conducted a cohort study to determine whether the consumption of gluten and casein results in an abnormally high level of peptides in the urine and blood of schizophrenic adults and autistic children. The subjects included 83 schizophrenic men (age 17-49), 37 schizophrenic women (ages 18-46), 128 autistic boys (ages 3.5-16), and 22 autistic girls (ages 3.5-14). Participants met DSM III criteria for his or her diagnosis. Laboratory data was collected from each subject and the same data was collected on control subjects who met similar age and sex characteristics. Data was collected on all subjects pre-intervention, at one month and three months after dietary intervention. Findings showed that 81% of the autistic children showed improvements in laboratory findings after three months of dietary intervention. Nineteen percent showed findings consistent with dietary error and continued gluten and casein consumption. Improvement was also noted after three months in the following behaviors: social isolation, eye contact, mutism, learning skills, hyperactivity, stereotypical activity, hygiene, panic attacks, and self mutilation. Strengths included the use of concrete laboratory findings and large sample sizes. Limitations were the short duration of dietary intervention and the fact that there wasn't a control group consisting of individuals who also carried a similar diagnosis.

Seung, Rogalski, Shankar, & Elder (2007) conducted a randomized, double blind crossover study to examine the effectiveness of a GFCF diet in children with ASDs in relation to verbal and nonverbal communication. Thirteen children (10 male and three female) between the ages two and 16 who had been diagnosed with autism participated. Diagnosis was based on the DSM-IV criteria for ASD. Videos of parent-child play interactions were used. Verbal exchanges were measured using the Systematic Analysis of Language Transcripts (SALT) and communication behaviors were analyzed using nonparametric (Friedman) tests. Results were as follows: *Verbal social exchanges* had means to include a baseline=16, GFCF=11, and regular diet=15; *verbal imitations* had means to include a baseline=3.85, GFCF=1.85, and regular diet=3.54; *number of words produced* had means to include a baseline=35, GFCF=32, and regular diet=37; and *total utterances* had means to include a baseline=42, GFCF=36, and regular diet=45. Strengths of the study included the fact that it is a double blind randomized clinical trial and food was prepared by one certified nutritionist for all participants. Limitations included a short intervention period, small sample size, and there was a large variance between baseline verbal abilities. Also this was a secondary analysis using existing data.

Knivsberg, Reichelt, Hoien, & Nodland (2002) conducted a single blind, randomized study to determine whether a GFCF diet may aid in enhanced learning for children diagnosed with autistic syndromes. They examined social, emotional, attention, communication, cognitive, sensory, and motor skills using standardized testing before and one year after diet implementation. A control group was utilized. Subjects included 20 children with autistic syndromes as well as abnormal urinary peptide patterns. Ages ranged from 59-127 months. Ten children were placed in the control group and 10 children utilized dietary intervention. The DIPAB (a Danish instrument for measuring autistic traits) was utilized to evaluate autistic

behavior, function of language, motor skills, communication, and social contact. Cognitive skills were measured using the Leiter International Performance Scale. Linguistic abilities were measured using the Illinois Test of Psycholinguistic Abilities and the Reynell Developmental Language Scale. Lastly, motor function was measured using the Movement Assessment Battery for Children. Many specific traits were examined based on the general behaviors of autism listed and every single trait showed marked improvement in the diet group when compared to the control group after one year of implementation. Strengths included a randomized, single blind study with a long implementation period. Inclusion criteria were utilized and educators were made available to parents throughout the study. Limitations on this study were that the sample size utilized was fairly small and it's possible the study could have been double blinded.

Whiteley et al (2010) conducted a two stage, 24 month, scanbrit randomized, controlled, single-blind study of a GFCF dietary intervention for children with autism spectrum disorders to evaluate and compare the effects of dietary interventions between a control and intervention group using a comprehensive assessment battery in children diagnosed with ASDs. The participants included 55 children with an ASD diagnosis. There were 26 children in the intervention group and 29 in the control group. Exclusion criteria for the study included any co-morbid diagnoses of epilepsy, fragile-X syndrome, tuberous sclerosis, developmental age below 24 months, or the use of pharmacologic therapy. Autism behaviors were assessed using the Autism Diagnostic Observation Schedule (ADOS) and Gilliam Autism Rating Scale (GARS). Developmental level was assessed using Vineland Adaptive Behavior Scale (VABS). Study members were blinded, but the parents were not blinded. Reassessments were performed at 8 and 12 months. The control group was then also placed on a GFCF diet from 12-24 months and reassessed. Improvement was seen after 12 months in core autistic behaviors for the intervention

group with ADOS P=0.0022, GARS P=0.0001, as well as improvements in inattention and hyperactivity. There was a plateau effect thereafter. Strengths of this study included the fact that exclusion criteria were utilized, the study took place over a sufficient amount of time to truly see changes, and study participants were blinded. Limitations included the fact that the study was not double blinded, children continued to receive alternative therapies, and the study was unable to identify potential best responders based on their history or characteristics.

Elder, Shankar, Shuster, Theriaque, Burns, & Sherrill (2006) conducted a randomized, double-blind repeated measures crossover design pilot study to determine the effects of a GFCF diet on the behaviors of autistic children and evaluate the effects of dietary intervention on urinary peptide levels. 15 children (12 boys and 3 girls), ages 2-16 with ASD were included in the study. Tools used to measure subject qualities included the Autism Diagnostic Interview-Revised (ADI-R), the Childhood Autism Rating Scale (CARS), Urinary Peptide Levels (UPL), and the Ecologic Communication Orientation (ECO) Language Sampling Summary. Data was collected prior to intervention, at week 6, and at week 12. Unfortunately, no significant changes were noted over the 12-week trial period. CARS $p = .85$, ECOS $p = .29$, behavioral frequencies $.32 < p < .45$, urinary peptide levels of gluten $p = .44$ and casein $p = .11$. Strengths included the fact that this was a randomized, double blind study and a placebo diet was used to keep parents blinded. Limitations included the small sample size used, the short duration of only 12 weeks, and the fact that dietary intervention was not performed in a controlled environment.

More recently, in 2015, two randomized double blind placebo controlled studies were performed although both studies lasted only a short period of time and did not produce positive results. One of the studies lasted only 7 days, which seems fairly pointless to even conduct, and the second lasted 12 weeks. The results are as follows.

The first study was conducted by Pusponegoro, Ismael, Firmansyah, Sastroasmoro, & Vandenplas (2015) to determine the effect of gluten and casein supplementation in children, who were previously GFCF, on maladaptive behavior, gastrointestinal symptom severity, and urinary I-FABP (intestinal fatty acid binding protein) excretion which is a marker for intestinal mucosal cell damage. Fifty children, ages 4.3-6.7 with ASD, who had severe maladaptive behavior and a urinary I-FABP value of > 96.97pg/mg creatinine, were included in the study. The Approach Withdraw Problems Composite (AWPC) was used to measure maladaptive behaviors pre and post gluten and casein exposure, the Gastrointestinal Symptom Severity Index (GSSI) was used to measure GI symptoms pre and post exposure, and Urinary I-FABP was measured pre and post exposure. The AWPC t-score decreased after supplementation in the placebo ($p < 0.001$) and intervention groups ($p < 0.001$). P=0.971 between the two groups. Both groups started with a GSSI of zero. After intervention, the median GSSI for the control group was 0 and median for the intervention group was 3. There was an increasing trend of I-FABP in the intervention group and a decreasing trend in the control group, yet changes between the two groups were not significantly different with p=0.416. The only strength noted for this study is that it was a randomized double-blind study. A fair number of limitations were noted that included a small sample size, short duration of gluten/casein consumption, the biscuits utilized as gluten/casein supplementation were probably not identical in taste, the chosen amount supplemented was arbitrary, the time between inclusion in study and introduction of dietary intervention varied, and outside therapies differed and were not considered for each child.

The second recent study was conducted by Hyman et al (2015) to obtain information on the safety and efficacy of the GFCF diet in children with autism. This was a 12-week double blind, placebo-controlled challenge study that included 14 children who were under the age of

six and diagnosed with Autistic Disorder, Asperger's Disorder, or Pervasive Developmental Disorder Not Otherwise Specified based on the criteria from the DSM-IV. Participants were required to be enrolled in a comprehensive Applied Behavior Analysis Intervention program for the duration of the study. Multiple scales and scoring methods were utilized to include: Autism Diagnostic Interview (ADI-R), Autism Diagnostic Observation Schedule (ADOS), Mullen Scales of Early Learning, Vineland Adaptive Behavior Scales, World Health Organization growth standards, laboratory testing for food allergies and vitamin deficiencies, the Bristol Stool Scale, the Conners Abbreviated Rating Scale, and the Ritvo-Freeman Real Life Rating Scales. Unfortunately, no significant findings were noted on active challenge days when compared to placebo challenge days. There are some notable strengths and weaknesses of this study. Strengths included the utilization of Registered Dieticians to monitor adherence to diet and nutritional intake, the fact that consumption of gluten and casein was carefully measured, there was consistency in all the children receiving Applied Behavior Analysis (ABA) therapy, and everyone was blinded to the challenges given. Limitations included the small sample size, the fact that only a 4-6 week complete GFCF diet was required prior to the challenges which may be too short to see initial changes, and the fact that administering gluten and/or casein challenges would seem to defeat the purpose of long term GFCF dietary intervention.

Harris & Card (2012) conducted a cross-sectional pilot study to evaluate the nutritional influences on GI symptoms and behavior patterns in children with ASD. Participants included 13 children, aged 5-12 years old diagnosed with an ASD, who were recruited from the Asperger's Support Network website. An online survey was conducted which included questions regarding general health, demographics, GI symptoms, behavior patterns, and a Food Frequency Questionnaire (FFQ). Gastrointestinal Symptoms Rating Scale (GSRS) was used to rate

abnormal GI symptoms, and the Childhood Autism Rating Scale (CARS) was used to rate behavior patterns. More than half of the children were already on a GFCF diet by parental choice. 53.8% of the children did experience postprandial GI symptoms according to the survey. Mean GSRS score was 19.2 and mean CARS score was 43.9 and unfortunately scores did not differ according to diet. However, 100% of the parents with children on a GFCF diet (n=7) reported improved GI and behavior patterns after diet implementation. A couple strengths for this study included the use of validated questionnaires and relative homogeneity of the sample. Limitations included the small sample size, the fact that the questionnaires were subjective, the uncertain ability of parents to quantify the severity of their child's symptoms, and the differences in parental implementation of the GFCF diet.

A more unique approach to studying dietary effects on children with ASD was conducted by de Magistris et al (2013) to challenge the hypothesis that dietary-derived non-self antigens could permeate impaired gut barrier and stimulate the immune system, affecting or increasing autism symptoms. Participants included 31 children with an ASD diagnosis currently following a GFCF diet for an average of 3 years, 131 children with an ASD diagnosis following a regular diet, and 44 healthy children utilized as matched controls. Data collected included intestinal permeability measurements and antibodies to food antigens. A statistical analysis was performed using the Mann-Whitney, the Kruskal-Wallis and Dunn's, and Fisher exact tests. Approximately twenty five percent of the enrolled ASD children had impaired intestinal barrier function. The GFCF diet appeared to normalize intestinal barrier impairment. Immune response was noted to be triggered by gluten and casein consumption in some ASD children. It is probable that determination of antibody titers to food antigens could be used to identify potential responders to the GFCF diet according to the study. Strengths of this study included the large sample size of

ASD children, the fact that control groups were present, and concrete laboratory evidence was utilized. Limitations included a smaller control group when compared to the study group, the fact that dietary intervention was not professionally monitored, and autism behavior symptoms specifically were not evaluated.

One last and the most recent case-control study that was examined was conducted by Mari-Bauset, Llopis-Gonzalez, Zazpe, Mari-Sanchis & Suarez-Varela (2016) to determine whether children with ASD on a GFCF diet vs. a regular diet have lower anthropometric measures, varied nutrient intake, and are less likely to meet daily-recommended intake values. Children ages 6-9 years old diagnosed with an ASD were enrolled in the study and the severity of autism symptoms was not considered (n=105). The study group consisted of 20 children and the control group consisted of 85 children. Height and weight measurements were utilized to calculate BMI. Caloric intake, macronutrients, and micronutrients were compared between the two groups. The Healthy Eating Index was utilized also to compare nutrients and Dietary Reference Intakes were utilized to measure adequate or inadequate intake. Overall, ASD children on a GFCF diet had lower BMI's than those on a regular diet. Vitamin and nutrient differences were noted between the two diets with the GFCF group being deficient in some nutrients but the regular diet group experienced deficiencies in other nutrients. Typically the GFCF diet group ate a "healthier" diet than their counterparts. Strengths included the children presented with similar characteristics in socioeconomic status, place of residence, ethnicity, and living conditions and the children were studied in parallel over the same time period. Limitations included a small sample size, the fact that only a 3-day food record was utilized, the GFCF diet was not monitored professionally, and autism behaviors or characteristics were not mentioned in this study.

Articles were reviewed and graded using the American Association of Critical-Care Nurses' (AACN) updated evidence-leveling system, which was revised in 2008. This upgraded system helps to alleviate confusion when compared to other grading systems, as the order of grading had originally been reversed compared to others. "Research designs identified in the new leveling system include meta-analysis, meta-synthesis (the qualitative counterpart to meta-analysis), randomized and nonrandomized studies, qualitative research, descriptive or correlational studies, systematic reviews, and integrative reviews" (Armola et al, 2009).

This grading system uses an alphabetical instead of numerical scale to further minimize confusion when compared with other systems. Letters range from A to M: A being the highest level of evidence to include meta-analyses and meta-syntheses with consistent results, and M referring to manufacturer's recommendations only (Armola et al, 2009). This grading system was chosen due to the broad range of description for hierarchy and the variability of the 15 studies examined. A synopsis of each study with its individual level of hierarchy grade can be found in the Appendix.

Discussion

Dissemination

Background information and theory as well as a summary of findings via poster was presented to a local pediatrician's office to encourage practicing physicians to include dietary recommendations in the care and treatment of children with an ASD. The poster was utilized since it was unlikely that the small family practice had the resources or space available to conduct a PowerPoint presentation. Time was allotted for discussion at the end of the presentation to answer questions and obtain opinions and feedback from the physicians and office staff. Finally, an anonymous survey was conducted to determine whether the physicians

and staff found the information useful and to determine whether they saw it plausible to include dietary recommendations in their treatment plans proceeding forward.

Three physicians, one physician's assistant, and two registered nurses were present for the presentation. Overall, the staff was not aware of dietary intervention for children with an ASD other than in cases where a true dietary allergy was present. The physicians and physician's assistant were skeptical to agree upon immediately recommending a GFCF diet to their patients. They did agree, however, to perform some more research independently in order to gain a broader understanding of dietary implications in children with an ASD. All agreed that they might possibly begin making the recommendation to parents in the future, so long as the parent understands that positive results are not guaranteed.

Interpretation

Eleven out of the 15 studies did show improvements in the symptoms being measured after eliminating gluten and casein from the subjects' diet (Hsu et al, 2009; Pennesi & Klein, 2012; Knivsberg et al, 2002; Whiteley et al, 2010; Cade et al, 2000; Harris & Card, 2012; de Magistris et al, 2013; Mari-Bauset et al, 2016; Genius & Lobo, 2014; Herbert & Buckley, 2013; Genius & Bouchard, 2010). The four studies that showed no significant improvement (Seung et al, 2007; Elder et al, 2006; Pusponegoro et al, 2015; Hyman et al, 2015) in any measured symptoms had small sample sizes, short durations of diet implementation, or dietary infractions as part of the study. Overall, better results had been reported after completing one full year of dietary intervention in the studies lasting that length of time (Cade et al, 2000; Hsu et al, 2009; Knivsberg et al, 2002; Whiteley et al, 2010; de Magistris et al, 2013; Genius & Lobo, 2014; Herbert & Buckley, 2013).

Many of these studies seem flawed in one way or another. A common theme among all of the studies is the difficulty in knowing whether strict adherence to the GFCF diet was successful without mistake, since all of the studies allowed the children to remain in their own home and continue with life as usual otherwise.

It would make sense that long term dietary change would need to take place in order to see major changes in neurologic or behavioral symptoms. Just as any other part of the human body, if damage has occurred to the GI tract due to the consumption of gluten or casein, it would only seem reasonable that healing of the GI tract would take time after complete removal of these proteins from the child's diet has been successfully accomplished.

Implications for Nursing

Although the body of evidence for this literature review is not 100% consistent, it is not without merit that the dietary intervention of removing gluten and casein from the autistic child's diet has the possibility of proving to be beneficial. Like any and every therapy or treatment for ASD's, a child may or may not respond positively to dietary intervention as children respond differently to every treatment option currently available (Whiteley et al, 2013). It is important for parents and physicians of children with autism to be aware of this possibility of gastrointestinal inflammation and central nervous system correlation. The hope is that increased awareness will lead to increased practice recommendations for dietary changes from practicing pediatricians to the parents of children affected by ASD.

Based on the findings of this review, the first desired practice recommendation to be made would be to disseminate findings and educate local developmental pediatric practices and county developmental agencies of the possible benefits of following a GFCF diet as well as the possible negative impact of gluten and/or casein consumption in autistic children. "Clinicians

working with families of individuals with ASD are often asked for advice and find themselves unable to offer the most up-to-date and scientifically credible information" (Elder, 2008, p.583). The fact that there is even some hope and proof that a simple dietary change could alleviate symptoms related to autism should be known by the clinicians that see and treat these children on a daily basis.

The American Family Physician (AFP) Strength of Recommendation Taxonomy (SORT) was utilized to review this recommendation. According to this system, "grades are assigned on the basis of quality and consistency of available evidence" (Ebell et al, 2004). This scale is intended to allow its use among various sources of evidence and is currently used by several medical journals. Recommendations are given a grade A, B, or C. The above recommendation is given a grade B for overall strength since results are inconsistent and studies are limited.

The second recommendation proposed would be to encourage these developmental pediatricians and local developmental agencies to include dietary change as a possible treatment option for children diagnosed with an ASD. Treatment recommendations generally include educational intervention, physical and developmental therapy, and behavioral treatment (Elder, 2008). Yet "there is increasing recognition that the expression of ASD in some sub-groups may also include a number of additional elements beyond psychiatry that may be potentially relevant" (Whiteley et al, 2010, p.88). Diet changes are under scrutiny as a physical trigger for psychological symptoms. The hypothesis that eliminating gluten and casein consumption proves beneficial in some way has been strengthened by the results of 11 of the 15 studies examined. It would only seem fair to offer desperate parents seeking answers any and every angle of treatment that is available to possibly benefit their children.

This practice recommendation is also given the strength of recommendation grade B using the SORT hierarchy due to the inconsistency of results and limited availability of evidence. It is important to note however, that every single autistic child is unique and no two are exactly alike. The diagnosis is termed autism spectrum disorder because there is an extremely large "spectrum" of symptoms that may be seen from child to child (Pennesi & Klein, 2012). Therefore, it is impossible to determine that any treatment option, including diet, will 100% be effective for all children diagnosed.

Implications for implementing the two proposed practice recommendations would be finding the time and appropriate resources and personnel to travel to local physician offices and developmental agencies. Also the reluctance of clinicians toward adopting new practice or recommendations could prove to be a barrier toward successful implementation. It would prove beneficial and probably more convincing for clinicians, if further research including larger sample sizes and longer duration paired with better control over interventions was conducted.

It is my hope that upon completion of my Master's in Nursing Education degree, I will be able to work directly with physicians who treat children with autism as well as educate the parents and families who are caring for these children. I hope to bring an increased awareness of alternative treatment options, including the GFCF diet, as well as conventional treatment options to the parents of children with autism.

Conclusion

Although the topic of dietary intervention for children with ASD seems to be growing, scientific information and evidence is still extremely limited. Studies vary in their methods, measurements, and results. Recommendations for future studies would include adequate control groups which mimic the intervention group, larger sample sizes overall, longer durations of

complete gluten and casein removal from the diet, and more concrete symptom measurement and evaluation versus parental input.

It is interesting and reassuring to know that there are new and alternative treatments being addressed for the growing number of autistic children present in our country today. Many parents are unsatisfied with current diagnosis standards and traditional treatment options (White, 2003). This may lead some to turn to many of the alternative treatments that are currently floating around without full knowledge of whether or not they will work. Yet although current literature is not fully supportive of the dietary removal of gluten and dairy as a guaranteed cure, current results may leave parents, physicians, and therapists hopeful and lean toward a probable benefit for many children.

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APPENDIX

Authors (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Pennesi, C.M. & Klein, L.C. (2012). Effectiveness of the gluten-free, casein-free diet for children diagnosed with autism spectrum disorder: based on parental report. Nutritional Neuroscience 15(2), 85-91	To evaluate whether the implementation of a gluten and casein free diet results in improvement in autistic behaviors, social behaviors, and GI symptoms in children with an autism spectrum disorder (ASD) diagnosis.	Longitudinal Survey Cohort Study	N=387 participants who were parents or primary caregivers of children with a clinical diagnosis of ASD. No exclusion criteria were identified.	A 90 item online questionnaire was administered to each participant. Diet implementation, compliance, and length of implementation was measured. Also included were parental reports of observable changes in their child's behaviors as well as gastrointestinal symptoms.	Results show that implementing a gluten and casein free diet may positively impact autistic behaviors and GI symptoms, specifically for those with previous GI symptoms and food allergies reported ($p<0.05$). Strict adherence seems to have a better outcome than those who have dietary errors even just on occasion.	**Strengths:** *Explanation of the purpose was clear. *Large sample size. *Participants were grouped by specific diagnosis as well as diet adherence. **Limitations:** *No exclusion criteria for participants. *Subjective survey could vary with each participant. *No control or methods regarding diet implementation.	AACN level of evidence: Grade C (Cohort Study with inconsistent results).

Authors (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Hsu, C.L., Lin, D.C.Y., Chen, C.L., Wang, C.M., & Wong, A.M.K. (2009). The effects of a gluten and casein-free diet in children with autism: a case report. Chang Gung Med J 32, 459-465.	To provide a detailed report of one child who showed significant improvements in autistic behaviors after implementing a gluten and casein-free diet.	Observational case-report	One child age 42 months at the initiation of the study, diagnosed with autism, growth and developmental retardation, and CHARGE syndrome.	Data was collected at 2.5 months, 5 months, and 11 months after initiation of diet implementation. The Chinese Child Developmental Inventory as well as the Bayley Scales of Infant Development were used to classify developmental ages in eight different areas of growth and development.	Improvement in all areas of development were noted at the 11 month mark of follow up as well as weight percentiles which were originally below the third percentile and had increased to approximately the 15th percentile.	**Strengths:** *Objective developmental measurement tools were utilized before and after interventions. *Intermittent follow up periods. *Long follow up. **Limitations:** *Single observed case report. *Double blind observations before and after initiation of diet were not performed. *Child continued to receive physical, occupational, speech, and sensory integration therapies.	AACN level of evidence: Grade E (single case report and no blindness used for evaluations).

Authors (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Seung, H., Rogalski, Y., Shankar, M., & Elder, J. (2007). The gluten- and casein-free diet and autism: communication outcomes from a preliminary double-blind clinical trial. Journal of Medical Speech-Language Pathology 15(4), 337-345.	To examine the effectiveness of a gluten and casein free diet in children with autism spectrum disorders in relation to verbal and nonverbal communication.	Randomized, double-blind crossover design study.	Thirteen children (10 male and three female) between the ages two and 16 who had been diagnosed with autism participated. Diagnosis was based on the DSM-IV criteria for autism spectrum disorder.	Videos of parent-child play interactions were used. Verbal exchanges were measured using the Systematic Analysis of Language Transcripts (SALT). Communication behaviors were analyzed using nonparametric (Friedman) tests.	*Verbal social exchanges:* Mean-baseline=16, GFCF=11, regular diet=15. *Verbal imitations:* Mean-baseline=3.85, GFCF=1.85, regular diet=3.54. *Number words produced:* Mean-baseline=35, GFCF=32, regular diet=37. *Total utterances:* Mean-baseline=42, GFCF=36, regular diet=45.	**Strengths:** *Randomized clinical trial. *Double-blind. *Food was prepared by one certified nutritionist for all participants. **Limitations:** *Short intervention period. *Small sample size. *Large variance between baseline verbal abilities. *A secondary analysis using existing data. *No control group used.	AACN Level of Evidence: Grade B (randomized double-blind study with consistent results).

Authors (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Knivsberg, K.M., Reichelt, K.L., Hoien, T., & Nodland, M. (2002). A randomized, controlled study of dietary intervention in autistic syndromes. Nutritional Neuroscience 5(4), 251-261.	To determine whether a gluten and casein free diet may aid in enhanced learning for children diagnosed with autistic syndromes.	Single blind, randomized study examined social, emotional, attention, communication, cognitive, sensory, and motor skills using standardized testing before and one year after diet implementation. Control group was utilized.	20 children with autistic syndromes as well as abnormal urinary peptide patterns. Ages ranged from 59-127 months. 10 children were placed in the control group and 10 children utilized dietary intervention.	DIPAB (standardized Danish scheme) utilized to evaluate autistic behavior, function of language, motor skills, communication, and social contact. Cognitive skills measured using the Leiter International Performance Scale. Linguistic abilities measured using the Illinois Test of Psycholinguistic Abilities and Reynells spraktest. Motor function measured using Movement Assessment Battery for Children.	Many specific traits were examined based on the general behaviors of autism listed. Every single trait showed marked improvement in the diet group when compared to the control group after one year.	**Strengths:** *Long implementation period. *Randomized, single blind study. *Inclusion criteria utilized. *Educators were available to parents throughout the study. **Limitations:** *Study could have been double blinded. *Small sample size.	AACN Level of Evidence: Grade B (randomized blinded study with consistent results).

Author (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Whiteley, P., Haracopos, D., Knivsberg, A., Reichelt, K. L., Parlar, S., Jacobsen, J., Seim, A., Pedersen, L., Schondel, M., & Shattock, P. (2010). The scanbrit randomized, controlled, single-blind study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders. Nutritional Neuroscience 13(2), 87-100.	To evaluate and compare the effects of dietary intervention between a control and intervention group using a comprehensive assessment battery in children diagnosed with autism spectrum disorders.	A randomized, controlled, single-blind, 2-stage/24 month study using the gluten and casein free diet.	Children with autism spectrum disorder diagnosis. N=26 in the intervention group and N=29 in the control group. Exclusion criteria: co-morbid diagnoses of epilepsy, fragile-X syndrome, tuberous sclerosis, developmental age below 24 months, pharmacologic therapy.	Autism behaviors assessed using Autism Diagnostic Observation Schedule (ADOS) and Gilliam Autism Rating Scale (GARS). Developmental level assessed using Vineland Adaptive Behavior Scale (VABS). Study members blinded. Parents not blinded. Reassessments performed at 8 and 12 months. Control group then placed on diet from 12-24 months and reassessed.	Improvement seen after 12 months in core autistic behaviors for intervention group. ADOS P=0.0022, GARS P=0.0001, as well as improvements in inattention and hyperactivity. Plateau effect thereafter.	**Strengths:** *Study participants blinded. *Sufficient length of time. *Exclusion criteria. **Limitations:** *Not double blinded. *Children continued to receive alternative therapies. *Study unable to identify potential best responders.	AACN Level of Evidence: Grade B (randomiz-ed, controlled study with consistent results).

Author (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Cade, R., Privette, M., Fregly, M., Rowland, N., Sun, Z., Zele, V., Wagemaker, H., & Edelstein, C. (2000). Autism and schizophrenia: intestinal disorders. Nutritional Neuroscience 3, 57-72.	To determine whether the consumption of gluten and casein results in an abnormally high level of peptides in the urine and blood of schizophrenic adults and autistic children.	Cohort study.	N=83 schizophrenic men (age 17-49), N=37 schizophrenic women (ages 18-46), N=128 autistic boys (ages 3.5-16), and N=22 autistic girls (ages 3.5-14). Participants met DSM III criteria for his or her diagnosis.	Laboratory tests were drawn from subjects as well as control subjects with similar age and sex pre-intervention, at one month and three months after intervention.	81% of the autistic children showed improvements in laboratory findings after three months of dietary intervention. 19% showed findings consistent with dietary error and continued gluten and casein consumption. Improvement also noted after 3 months in the following behaviors: social isolation, eye contact, mutism, learning skills, hyperactivity, stereotypical activity, hygiene, panic attacks, and self mutilation.	**Strengths:** *Concrete laboratory findings. *Large sample sizes. **Limitations**: *Short duration. *No control group for diagnosed individuals. *No blinding.	AACN Level of Evidence: Grade C (correlational cohort study with consistent results).

Author (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Elder, J. H., Shankar, M., Shuster, J., Theriaque, D., Burns, S., & Sherrill, L. (2006). The gluten-free, casein-free diet in autism: results of a preliminary double blind clinical trial. Journal of Autism and Developmental Disorders 36(3), 413-420.	To determine the effects of a gluten-free, casein-free diet on the behaviors of autistic children and evaluate the effects of dietary intervention on urinary peptide levels.	Randomized, double-blind repeated measures crossover design pilot study.	15 children, ages 2-16 with autism spectrum disorder (12 boys and 3 girls).	Tools used to measure subject qualities included: Autism Diagnostic Interview-Revised (ADI-R), Childhood Autism Rating Scale (CARS), Urinary Peptide Levels (UPL), and Ecologic Communication Orientation (ECO) Language Sampling Summary. Data was collected prior to intervention, at week 6, and at week 12.	No significant changes in findings over 12 week trial period. CARS $p=.85$, ECOS $p=.29$, behavioral frequencies $.32<p<.45$, urinary peptide levels of gluten $p=.44$ and casein $p=.11$.	**Strengths:** *Randomized, double-blind study. *Placebo diet used to keep parents blinded. **Limitations:** *Small sample size. *Short duration. *Dietary intervention was not in a controlled environment.	AACN Level of Evidence: Grade C (randomized controlled study with inconsistent results).

Author (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Pusponegoro, H.D., Ismael, S., Firmansyah, A., Sastroasmoro, S., Vandenplas, Y. (2015). Gluten and casein supplementa-tion does not increase symptoms in children with autism spectrum disorder. Acta Paediatrica, 104, e500-e505.	To determine the effect of gluten and casein supplementa-tion in children who were previously GFCF, on maladaptive behavior, gastrointes-tinal symptom severity, and urinary I-FABP excretion.	Randomized, double-blind, placebo controlled trial.	50 children, ages 4.3-6.7 with ASD who had severe maladaptive behavior and a urinary I-FABP value of > 96.97pg/mg creatinine.	The AWPC (Approach Withdraw Problems Composite) was used to measure maladaptive behaviors pre and post gluten and casein exposure, the GSSI (Gastrointes-tinal Symptom Severity Index) was used to measure GI symptoms pre and post exposure, and Urinary I-FABP was measured pre and post exposure.	AWPC *t*-score decreased after supplementation in placebo ($p < 0.001$) and intervention groups ($p < 0.001$). $p=0.971$ between the two groups. Both groups started with a GSSI of zero. After intervention, the median GSSI for the control group was 0 and median for the intervention group was 3. There was an increasing trend of I-FABP in the intervention group and a decreasing trend in the control group, yet changes between the two groups were not significantly different with $p=0.416$.	**Strengths:** *Randomized double-blind study. **Limitations:** *Small sample size. *Short duration of gluten/casein consumption. *Biscuits utilized as gluten/casein supplementa-tion were probably not identical in taste. *Chosen amount supplemented was arbitrary. *Time between inclusion in study and introduction of dietary intervention varied. *Outside therapies differed and were not considered for each child.	AACN Level of Evidence: Grade C (randomized double-blind study with inconsistent results).

Author (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Harris, C., Card, B. (2012). A pilot study to evaluate nutritional influences on gastrointes-tinal symptoms and behavior patterns in children with Autism Spectrum Disorder. Complemen-tary Therapies in Medicine, 20, 437-440.	To evaluate the relationship between GI symptoms and behavior patterns, and the influence of a GFCF diet on these issues in children diagnosed with ASD.	Cross-sectional study.	13 children aged 5-12 years old diagnosed with an ASD, who were recruited from the Asperger's Support Network website.	Online survey included questions regarding general health, demographics, GI symptoms, behavior patterns, and a Food Frequency Questionnaire (FFQ). Gastrointestinal Symptoms Rating Scale (GSRS) was used to rate abnormal GI symptoms, and the Childhood Autism Rating Scale (CARS) was used to rate behavior patterns.	More than ½ of the children were on a GFCF diet by parental choice. 53.8% of the children experienced post prandial GI symptoms. Mean GSRS score was 19.2 and mean CARS score was 43.9. Scores did not differ according to diet. However, 100% of the parents with children on a GFCF diet (n=7) reported improved GI and behavior patterns after diet implementation.	**Strengths:** *Use of validated questionn-aires. *Relative homogeneity of the sample. **Limitations:** *Small sample size. *Subjective questionn-aires. *Uncertain ability of parents to quantify the severity of their child's symptoms. *Differences in parental implementa-tion of GFCF diet.	AACN Level of Evidence: Grade C (Cross-sectional survey study with inconsistent results).

Author (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Hyman, S.L., Stewart, P.A., Foley, J., Cain, U., Peck, R., Morris, D.D., Wang, H., & Smith, T. (2015). The gluten-free/casein-free diet: a double-blind challenge trial in children with autism. Journal of Autism and Developmen-tal Disorders, 46(1), 205-220.	To obtain information on the safety and efficacy of the gluten-free/casein-free diet in children with Autism.	A 12-week double-blind, placebo-controlled challenge study.	14 children who were under the age of 6 and diagnosed with Autistic Disorder, Asperger's Disorder, or Pervasive Developmen-tal Disorder Not Otherwise Specified based on the criteria from the Diagnostic and Statistical Manual of Mental Disorders 4th Edition. Participants were required to be enrolled in a comprehensive Applied Behavior Analysis Intervention program for the duration of the study.	Multiple scales and scoring methods were utilized to include: Autism Diagnostic Interview (ADI-R), Autism Diagnostic Observation Schedule (ADOS), Mullen Scales of Early Learning, Vineland Adaptive Behavior Scales, World Health Organization growth standards, laboratory testing for food allergies and vitamin deficiencies, the Bristol Stool Scale, the Conners Abbreviated Rating Scale, and the Ritvo-Freeman Real Life Rating Scales.	No significant findings on active challenge days when compared to placebo challenge days.	**Strengths:** *Utilized Registered Dieticians to monitor adherence to diet and nutritional intake. *Consumption of gluten/casein was carefully measured. *Children were receiving consistent ABA therapy. *Everyone was blinded to challenges given. **Limitations:** *Small sample size. *4-6 week complete GFCF diet prior to challenges may be too short to see initial changes. *Administering gluten and/or casein challenges defeats purpose of long term GFCF diet.	AACN Level of Evidence: Grade C (Double-blind placebo-controlled challenge study with inconsistent results).

Author (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
de Magistris, L., Picardi, A., Siniscalco, D., Riccio, M.P., Sapone, A., Cariello, R., Abbadessa, S., Medici, N., Lammers, K.M., Schiraldi, C., Iardino, P., Marotta, R., Tolone, C., Fasano, A., Pascotto, A., Bravaccio, C. (2013). Antibodies against food antigens in patients with autistic spectrum disorders. BioMed Research International, 1-11.	To challenge the hypothesis that dietary-derived nonself antigens could permeate impaired gut barrier and stimulate the immune system, affecting or increasing autism symptoms.	Evaluation of anti-body prevalence in study group, control group, and neurotypical group.	31 children with an ASD diagnosis currently following a GFCF diet for an average of 3 years, 131 children with an ASD diagnosis following a regular diet, and 44 healthy children utilized as matched controls.	Intestinal permeability measurements, antibodies to food antigens, statistical analysis using Mann-Whitney, Kruskal-Wallis and Dunn's, and Fisher exact tests.	25.6% of the enrolled ASD children had impaired intestinal barrier function. GFCF diet appears to normalize barrier impairment. Immune response is triggered by gluten and casein in some ASD children. Determination of antibodies titers to food antigens could be used to identify potential responders to the GFCF diet.	**Strengths:** *Large sample size of ASD children. *Control groups present. *Concrete laboratory evidence utilized. **Limitations:** *Smaller control group. *Dietary intervention not professionally monitored. *Autism behavior symptoms not evaluated.	AACN Level of Evidence: Grade B (Well designed study with consistent results).

Author (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Mari-Bauset, S., Llopis-Gonzalez, A., Zazpe, I., Mari-Sanchis, A., Suarez-Varela, M.M. (2016). Nutritional impact of a gluten-free casein-free diet in children with autism spectrum disorder. Journal of Autism and Developmental Disorders, 46, 673-684.	To determine whether children with ASD on a GFCF diet vs. a regular diet have lower anthropometric measures, varied nutrient intake, and are less likely to meet daily-recommended intake values.	Case-control study.	Children ages 6-9 years old diagnosed with an ASD, severity not considered (n=105). Study group n=20 and control group n=85.	Height and weight measurements utilized to calculate BMI. Caloric intake, macronutrients, and micronutrients compared between two groups. Healthy Eating Index utilized also to compare nutrients. Dietary Reference Intakes utilized to measure adequate or inadequate intake.	ASD children on a GFCF diet had lower BMI's than those on a regular diet. Vitamin and nutrient differences were noted between the two diets with GFCF kids being deficient in some nutrients and regular diet kids being deficient in others. Typically the GFCF diet group at a "healthier" diet than their counterparts.	**Strengths:** *Children presented with similar characteristics in socioeconomic status, place of residence, ethnicity, and living conditions. *Children studied in parallel over same time period. **Limitations:** *Small sample size. *Only a 3-day food record was utilized. *GFCF diet not monitored professionally. *Autism behaviors or characteristics not mentioned in this study.	AACN Level of Evidence: Grade C (Case-control study with inconsistent results).

Author (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Genius, S.J. & Lobo, R.A. (2014). Gluten sensitivity presenting as a neuropsychiatric disorder. Gastroenterology Research and Practice, 1-6.	To provide a clinical review of gluten sensitivity as it relates to mental health and to examine pathophysiological mechanisms for the neuropsychiatric symptoms associated with gluten sensitivity in some patients.	Case-report.	A 23-year-old female with a longstanding history of auditory and visual hallucinations.	Symptom review following a regular diet, gluten free diet, and after accidental gluten exposure.	The subject experienced extreme auditory and visual hallucinations throughout her entire life as well as being diagnosed with irritable bowel syndrome. In college she decided to independently eliminate gluten from diet with complete resolution of symptoms. Symptoms would return within hours of any slight accidental gluten exposure and last 24-72hrs.	**Strengths:** *Symptoms completely resolved after gluten elimination-providing clear correlation. *Subject was not cognitively delayed and able to give accurate description of symptoms. **Limitations:** *No concrete laboratory data utilized as subject refused. *Physician monitoring not mentioned.	AACN Level of Evidence: Grade E (Single case-report without concrete evaluation methods).

Author (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Herbert, M.R., Buckley, J.A. (2013). Autism and diet therapy: case report and review of the literature. Journal of Child Neurology, 28(8), 975-982.	To provide a report of a child who experienced regressive autism at the age of 4, subsequently placed on a gluten-free casein-free diet, and followed into teenage years.	Case-report.	A 13-year-old child who experienced regressive autism at age 4 and later diagnosed with epilepsy at age 11 with limited response to typical interventions.	The Childhood Autism Rating Scale (CARS) was utilized to score autism severity. Symptoms and interventions were detailed and recorded in chronological order.	Autism symptoms significantly improved on a GFCF diet and after puberty seizure activity was significantly improved on a GFCF ketogenic diet.	**Strengths:** *Symptoms and interventions are detailed chronologically. *EEG performed pre and post further dietary intervention. *CARS scores noted pre and post interventions. **Limitations:** *Cause of significant regression into autism in a previously neurotypical 4-year-old is not mentioned. *Biomedical supplements were also being utilized and changed throughout treatment. *Information source not mentioned.	AACN Level of Evidence: Grade E (Single case-report with unknown source of information).

Author (Year) Title Publication	**Purpose**	**Design**	**Sample**	**Data Collection and Measurement**	**Findings**	**Strengths and Limitations**	**Level of Evidence**
Genius, S.J., Bouchard, T.P. (2010). Celiac disease presenting as autism. Journal of Child Neurology, 25(1), 114-119.	To describe a case where a 5-year-old boy presented with severe autism, later diagnosed with Celiac Disease whose autism symptoms resolved following a gluten-free diet.	Case-report.	A 5-year-old boy diagnosed with severe autism at age 3 who also experienced multiple abnormal gastrointestinal symptoms.	Symptom review and parental report before and after dietary interventions.	After 3 months following a gluten-free diet, the child is mainstreamed back into a regular education classroom without any individualized special education, and his autism symptoms have disappeared.	**Strengths:** *Concrete laboratory data utilized. **Limitations:** *Source of information unknown. *Follow up biochemical nutritional testing declined by parents due to resolution of symptoms.	AACN Level of Evidence: Grade E (Single case-report with unknown source of information).