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Abstract

In autism spectrum disorders, many parents resort to alternative treatments and these are generally perceived as risk free. Among these, the most commonly used is the gluten-free, casein-free diet. The objective of this work was to conduct a systematic review of studies published from 1970 to date related to the gluten-free, casein-free diet in autism spectrum disorder patients. Few studies can be regarded as providing sound scientific evidence since they were blinded randomized controlled trials, and even these were based on small sample sizes, reducing their validity. We observed that the evidence on this topic is currently limited and weak. We recommend that it should be only used after the diagnosis of an intolerance or allergy to foods containing the allergens excluded in gluten-free, casein-free diets. Future research should be based on this type of design, but with larger sample sizes.

Keywords

gluten-free, casein-free diet, autism, autism spectrum disorders (ASDs), review

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Autism spectrum disorders are a clinically characterized by difficulties with reciprocal social interactions; verbal and nonverbal communication deficiencies; and restricted, repetitive, and stereotyped behaviors and interests.¹ According to a recent publication analyzing 2008 data,² the prevalence has increased to 11.3 per 1000 people, and it is notably more common in men (ratio 4:1). On the other hand, no significant differences have been reported as a function of socioeconomic level or cultures.³

Gluten-Free, Casein-Free Diet: Background

So far, there are no curative treatments for this disorder; however, there is some hope of advances.⁴ In this context, many parents have turned to alternative treatments⁵⁻⁷ driven by the frustration and concern caused by the diagnosis rather than with sound justification, and this issue is compounded by the fact that the treatments are generally thought to be risk-free. These alternative treatments include the adoption of elimination diets, in particular the gluten-free, casein-free diet,⁸ the focus of this paper.

In relation to this, the elimination of gluten implies the exclusion of all food items containing wheat, oats, barley or rye, that is, all flours, bread, rusks, pasta, pastries, and other bakery products made with these cereals, while the elimination of casein means no intake of dairy products: milk, including

breast milk, yogurt, cheese, butter, cream or ice cream, among others.

On the other hand, in relation to children with autism spectrum disorders, these diets involve significant changes to their routine and such changes can, in themselves, affect their eating behaviors.⁹⁻¹¹ Additionally, the adoption of elimination diets works against efforts to improve the social integration of such children, in that a personal diet is an isolating factor.¹²

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Opioid Theory for Autism Spectrum Disorders

The most commonly cited theory to justify adoption of a gluten-free, casein-free diet is related to neurotransmitters¹³ and concerns the release of peptides with an opioid activity in the intestines. After digestion, certain types of proteins could cross the intestinal mucosa intact,¹⁴ if this were more permeable than normal—this being the case when it is impaired by immunologic factors or by lesions in the case of celiac disease. If these peptides, transported by the bloodstream, were to cross the blood-brain barrier and reach the central nervous system in large quantities, it would affect brain functioning.¹⁵ The hydrolysis of proteins from cereals and milk would generate exogenous neuropeptides (exorphins) such as gluteomorphins from gluten and beta-casomorphins from casein.

It should, however, be highlighted that exorphins have a low affinity for opioid receptors and that in dietary proteins there are also amino acid sequences with antagonist activity on opioid receptors which, despite having been known of for many years, tend not to be considered in this context.¹⁶

What is more, experiments have failed to find abnormally high concentrations of opioid peptides in either plasma or the nervous system of patients with autism spectrum disorders.¹⁷ As for urinary excretion, urinary opioid peptides have not been detected in people with autism spectrum disorders using modern methods with great sensitivity and specificity (namely, mass spectrometry coupled with high-performance liquid chromatography).¹⁸⁻²⁰

Prevalence

The adoption of gluten-free, casein-free diet, as an alternative treatment, is a poorly studied phenomenon. In the literature, figures are highly variable, indicating that this approach is tried in 20% to 70% of cases. For instance, Harrington et al⁶ reported rates of 66%; Wong et al,²¹ 30%; Herndon et al,²² 31.1%; Bandini et al,²³ 20.7%; and Hall et al²⁴ and Sharp et al,²⁵ 30%.

Behavior and Physiological Perspective

The first author to establish an association between the frequency and severity of schizophrenia and the intake of foods containing gluten and dairy products was Dohan: the foods' withdrawal improved symptoms and their reintroduction worsened them.^{26,27} Subsequently, Panksepp²⁸ suggested that the behavioral changes associated with autism were the result of an abnormal activation of the opioid system because of an excess of agonists in the brain. It has been considered that gluten from cereal and casein from dairy products could be responsible, as they are a source of "exorphins," peptides with opioid activity.²⁹⁻³²

Considering publications since 1970, excluding theses or book chapters, we found relatively few original studies on elimination diets that analyze the impact of foods on behavior in autism spectrum disorders. Several of these studies demonstrated significant improvements in intervention vs control

groups, and Whiteley et al³³ reported the appearance of a possible diet-related autism phenotype that seems to be emerging supportive of a positive dietary effect with slight improvement in certain groups with autism spectrum disorders. On the other hand, Sponheim¹² did not observe any improvement after introduction of the elimination diet, but rather behavioral regression due to stigmatization. Elder et al³⁴ and Seung et al³⁵ did not find any improvement in the behavior of participants in the intervention group.

Having discussed the questionable effectiveness of this nutritional intervention on cognitive-behavioral function, we will now assess its safety. Cornish¹¹ did not find any significant nutritional differences between children with autism spectrum disorders as a function of whether they were on the gluten-free, casein-free diet, similar to the findings of Johnson et al.³⁶ On the other hand, Arnold et al³⁷ observed a significantly lower concentration of amino acids, including tryptophan in children with autism spectrum disorders on gluten-free, casein-free diets. Higher homocysteine levels have been observed in patients on a gluten-free diet long-term compared to typically developing children, and this implies deficiencies in folates and vitamin B₆, increasing cardiovascular risk in the medium and long term.³⁸⁻⁴⁰ Mariani et al⁴¹ reported that patients on a gluten-free diet had high intakes of proteins and lipids but low intakes of carbohydrates, fiber, calcium, and iron. In line with this, Marcason^{42,43} warns about the risk of gluten-free diets resulting in deficient intake of both macro- and micronutrients, the associated restrictions making it much more difficult to achieve a balanced diet than when a broader variety of foods are consumed.

Similarly, a casein-free diet could result in calcium deficiency.⁴⁴⁻⁴⁷ Aldamiz-Echevarria et al⁴⁸ indicated that 76% of patients on a casein-free diet had a total lipid intake within the recommended range, but 85% had high ratios of $\omega 6/\omega 3$ and low plasma levels of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), a similar pattern being described by Schuchardt et al.⁴⁹ Further, slower bone development was observed in children with autism spectrum disorders on a casein-free diet than among those without dietary restrictions,⁵⁰ while Neumayer et al⁵¹ demonstrated that children with autism spectrum disorders had a lower bone density than controls. In this latter study, the total energy and macronutrient intakes did not differ significantly between groups, but the intakes of vitamin D and calcium were lower in children with autism spectrum disorders and this can be attributable to lower consumption or even the elimination of milk and other dairy products.

All the above justifies this systematic review of the studies published since 1970 concerning dietary restriction and its impact on autism spectrum disorders. Specifically, the objectives of this study were to determine, on the basis of the available scientific data, (1) the apparent efficacy and (2) any possible associated metabolic risks of dietary restrictions.

Methods

We conducted a systematic review of the medical literature related to gluten-free, casein-free type diets. The date of the last search was

Table 1. Levels of Evidence.

Levels of evidence	Characteristics
1	
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2	
2++	High-quality systematic reviews of case-control or cohort or studies.
2+	High-quality case-control or cohort studies with a very low risk of Confounding, bias, or chance and a high probability that the relationship is casual
2–	Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is casual
3	Nonanalytic studies, eg, case reports, case series
4	Expert opinion

Abbreviation: RCT, randomized controlled trial.

Source: SIGN, Scottish Intercollegiate Guidelines Network (2008).

Table 2. Grades of Recommendation.

Grades of recommendation	Definition
A	At least 1 meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Abbreviation: RCT, randomized and controlled trial.

Source: SIGN, Scottish Intercollegiate Guidelines Network (2008).

September 30, 2013. We based our search on the Medline database, in accordance with the proposals of the Spanish National Health System. In addition, we also consulted other databases: Cochrane Library, Scielo, ScienceDirect, and Embase. For the searches, we used the keywords *gluten-free*, *casein-free diet*, *autism*, *Autism Spectrum Disorders (ASDs)*, and *review*, with the corresponding Boolean operators. This paper complies with the methodological norms established for the publication of systematic reviews^{52,53} and the PRISMA recommendations.⁵⁴

We first retrieved systematic reviews and full original articles published from 1970 to 2013. These publications were then included in the analysis provided that the participants, of any age, met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, criteria for autism spectrum disorders; that they were put on a diet excluding gluten, casein or both; and that the outcome variables were related to the potential biomedical or behavioral symptoms of autism spectrum disorders. We did not restrict the searches by language. On the other hand, studies in which the diet was not under supervision of the researchers and any that did not report on health outcomes were excluded.

To guide the evaluation of the data in the papers retrieved, we defined levels of evidence, on the basis of their methodological quality in terms of the study design. We then established grades of recommendations for the

planning of dietary guidelines for patients with autism spectrum disorders. For this classification of the evidence and recommendations, we employed an instrument proposed by the Scottish Intercollegiate Guidelines Network.⁵⁵ The scale proposes that 2 characteristics of the source be used for assessing the quality of the scientific evidence provided (level of evidence): the study design and the risk of bias. Numbers from 1 to 4 are used to rate the study design, whereas signs (+++, +, and –) indicate the assessed risk of bias, according to the degree of fulfillment of key criteria related to this potential risk (Table 1). Based on this assessment of the quality of the scientific evidence in the source, grades are used (Table 2) to classify the strength of associated recommendations (A, B, C, and D).

In addition to the aforementioned system of levels, we considered the following features, as applicable, to assess the level of evidence provided by the selected articles: (A) Degree of homogeneity of the group studied (as determined by definitions and criteria applied); (B) use of a control group and the appropriateness of the selection; (C) type of experimental design (randomized or not); (D) knowledge of the intervention by patients, relatives, and other observers (open, simple or double blind trial); (E) nature of the dietary regimen (level of strictness) and degree of adherence; (F) selection of assessment criteria, including the instruments used (questionnaires, scales, etc.), for assessing changes in patient status under the treatment; and (G) the presence of confounding factors including any types of pharmacologic

Table 3. Studies Considering the Effectiveness of the Gluten-Free, Casein-Free Diet.

Author	N	Design	Assessment criteria	Results	LE ^a	GR
Goodwin et al, 1971 ⁶²	Cases: 15 children with ASDs Age: 6-13 y; controls: 14; siblings: 1-13 y	Cross-over intervention with gluten load test after GF diet; randomized; open-label; experimental	Blood biochemistry; EEG; behavioral	Correlation between autism and malabsorption, and between gluten sensitivity and cognitive impairment	3	D
Bird et al, 1977 ⁶³	9-y-old child with ASD; no controls	Case report; GFCF diet; experimental	Behavioral	Diet does not affect behavior	3	D
ÓBannion et al, 1978 ⁶⁴	1 child with ASD; no controls	Descriptive; case report	Behavioral; dietary restriction	Wheat, maize, tomatoes, sugar, mushrooms, and dairy products cause behavioral problems in the child	3	D
McCarthy et al, 1979 ⁶⁵	8 patients with ASD; unknown age; no healthy controls	Open label; gluten load after GF diet	Clinical picture and intestinal biopsy	No abnormal histologic findings in the intestine; no association between autism and celiac disease	2-	
Reichelt et al, 1990 ⁶⁶	15 patients with ASDs; 3-17 y old	Open label; urinary peptide levels; GFCF/GF/CF; cohort study	Peptiduria; Parent and caregivers questionnaire with retrospective comparison	Behavioral improvement after the treatment in more than 50% of children	3	D
Knivsberg et al, 1990 ²⁹	15 patients with ASD; age 6-14 y; no healthy control group	Open label; urinary peptide levels; GF/CF; cohort study	Parent and caregiver reports; standardized assessment questionnaires	Early improvement (first 6 mo), less evident after 1 y	3	D
Sponheim, 1991 ¹²	4 adults and 3 children with ASDs; 6-month GF diet	Experimental; randomized; double blind (gluten-free or placebo 1 y); cohorts	Parent and caregiver reports; standardized assessment questionnaires	No behavioral improvement	2++	B
Lucarelli et al, 1995 ⁶⁷	36 patients with ASDs, 8-13 y old; controls: 20 children without ASDs for the casein load test; 2-month CF diet	Open label before and after dietary restriction; casein load test; double blind, placebo-controlled cohort study	Standardized assessment questionnaire; measurement of Ig levels	After the dietary restriction, decrease in the specific Ig levels; behavioral improvement; casein load test results not conclusive	2-	
Knivsberg et al, 1995 ⁶⁸	Continuation of the authors' previous study; cf. Knivsberg et al, 1990	Experimental; open label; urinary peptide levels; GF/CF; cohort study	Peptiduria; parent and caregiver reports; standardized assessment questionnaires	No clear improvement after 1 y	3	D
Adams et al, 1997 ⁶⁹	1 boy and 1 girl with ASDs; both 3 y old	Series of cases: (1) very high doses of Mg + vitamin B ₆ ; (2) GFCF for 2 y	Parents report	Anecdotal improvement of the general behavior	3	D
Knivsberg et al, 1999 ⁷⁰	Girl with an ASD; 7 y old	Case report; GF for 2 y; experimental.	Parents report; standardized assessment questionnaires	Behavioral improvement in communication and socializing	3	D

(continued)

Table 3. (continued)

Author	N	Design	Assessment criteria	Results	LE ^a	GR
Whiteley et al, 1999 ⁹	Cases: 5 children with ASDs and 9 children with autism; no randomized controls; 6 children, all diagnosed with autism, formed a control group of children not involved with any dietary intervention; GF > 6 mo	GF diet for 5 mo; experimental; cohort study	Peptiduria; parents report; standardized assessment questionnaires	Behavioral improvement	2–	
Cade et al, 2000 ¹⁰	150 children with ASDs aged between 3.5 and 16 y; no healthy controls	Open label; gluten load test after GF diet; experimental	Behavioral; peptiduria	Improvement of the autistic signs and symptoms	2–	
Knivsberg et al, 2002 ⁷¹	Cases: 10 children with ASDs, GFCF diet for a y; controls: 10 children with ASDs with normal diet; both groups with a mean age of 7.5 y	Randomized; simple blind; GFCF diet for 1 y; experimental	Parents and caregiver report; standardized assessment questionnaires	Behavioral improvement in communication and socializing	2+	C
Elder et al, 2006 ³⁴	15 people with ASDs; aged 2–16 y old; GFCF diet for 12 wk; no healthy controls	Randomized, retrospective, double blind, cross-over (RCT), 6 wk under normal and GFCF diet, alternately	Parents report. Standardized assessment questionnaires; urinary peptide levels	No statistically significant differences were observed	2++	B
Irvin 2006 ⁷²	1 boy with an ASD, 12 y old	Case report, GFCF for 4 d	Direct observation of the level of aggression and destructive behavior	No behavioral change	3	D

Table 3. (continued)

Author	N	Design	Assessment criteria	Result	LE	GR
Patel and Curtis, 2007 ⁷³	10 children with ASDs and ADHD aged between 4 and 10 y old; no healthy controls	Open label, Experimental. Children received an integrated treatment based on nutritional (GFCF) and environmental changes, plus the chelating agents, for 3-6 months, as well as the usual behavioral therapy and physiotherapy	Behavioral assessment by physicians/ parents teachers; urinary heavy metals.	Lower urinary concentration of heavy metals; parents report a behavioral improvement	3	D
Seung et al, 2007 ³⁵	13 children with ASDs; 2-16 y old; no healthy controls	Retrospective, randomized, double blind, cross over study; 6 wk on a normal and GFCF diet, alternately	Video recording; assessment of verbal and nonverbal communication	No statistically significant differences were observed	2++	B
Millward et al, 2008 ⁵⁹		Systematic review		There is no empirical evidence base for recommending the GFCF diet	I+	A
Hyman et al, 2010 ⁵⁶	30 children with ASDs; 30-45 mo	Experimental; double blind; cross-over; RCT; 18 wk under GFCF and normal diet alternately	Behavioral assessment	No significant differences in the preliminary results (2010); no empirical evidence to recommend the GFCF diet	I+	A
Mulloy et al, 2010 ⁶⁰		Systematic review		No empirical evidence to recommend the GFCF diet	I+	A
Whiteley et al, 2010 ⁷⁴	72 children with ASDs; no healthy controls	Single-blind, randomized, clinical trial; grouped by ages, stratified; conducted in 2 phases	Standardized assessment questionnaires; peptiduria	Significant improvement in some ASD subgroups	2+	C
Mulloy et al, 2011 ⁶¹		Systematic review		Confirmation of the conclusions reached by Whiteley et al (2010)	I+	A
Harland 2012 ⁵⁷	In the recruitment phase, estimated number patients with ASDs 30; aged between 2 and 17 y	Experimental; double blind; cross over; RCT; 18 wk on GFCF and normal diet, alternately	Behavioral assessment (activity, sleep, behaviors related to the ASD); stool pattern; nutrition	Not yet complete	-	-

Abbreviations: AA: amino acids; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CF, casein free; GF, gluten free; GFCF, gluten-free, casein-free; GR, grade of recommendation; Ig, immunoglobulin; LE, level of evidence; RCT, randomized controlled trial.

^aThe studies classified as I- or 2- were not used in the recommendation process given the high risk of bias.

Table 4. Studies Considering the Safety of the Gluten-Free, Casein-Free Diet.

Author	N	Design	Assessment criteria	Result	LE ^a	GR
Cornish et al, 2002 ¹¹	Cases: 8 children with ASDs, 3-16 y old, GFCF diet; controls: 29 children with ASDs, 3-16 y old with no dietary restrictions	Retrospective, case-control	3-d food diary	No differences observed for energy and macro- and micronutrients	2-	
Black et al, 2002 ⁴⁴	Cases: 50 children who refuse milk (CF), controls 200 children who drink milk. Age range in both groups: 3-10 y	Observational, cross-sectional	4-d food diary; food frequency questionnaire; measurement of bone density	Lower intake of calcium; stature and bone density associated with CF diet	2-	
Arnold et al, 2003 ³⁷	Cases: 36 children with ASDs, 26 with normal diet, 10 with GFCF diet; controls: 24 without ASD, both groups under 5 y of age	Observational, cross-sectional	Blood analysis	Significant deficiency in AA (mainly tryptophan) associated with ASDs compared to controls, more pronounced on a GFCF diet	2+	C
Monti et al, 2007 ⁴⁵	One 8-y-old child	Case report	Dairy product elimination diet	Lower bone density	3	D
Konstantynowicz et al, 2007 ⁴⁶	Cases: 91 children with fractures; controls: 273 children without fractures; age range: 2.5-20 y	Observational; grouped by age and sex; randomized; case-control.	24-hour recall; bone density	Lower calcium intake and bone density in children with restriction of dairy products; weak association between fractures and milk consumption	2++	B
Hediger et al, 2008 ⁵⁰	75 children with ASDs on a CF diet; no controls	Observational; cross-sectional.	Cortical bone density	Reduced	2++	B
Johnson et al, 2011 ³⁶	22 children with ASDs aged 3-5 y; cases: 8 children on a GFCF diet for 3 mo; controls: 14 children with no dietary restrictions	Prospective, randomized, open-label cohort trial	24-h recall	No significant differences for proteins, lipids, carbohydrates, calcium, and iron	2-	
Neumayer et al, 2012 ⁵¹	Cases: 18 children with ASD; controls: 19 typically developing children; age range in both groups 8-14 y	Observational; case-control	Bone mineral density; analysis of blood and saliva; physical exercise; 3-d food diary	Lower bone density; lower physical activity; lower intake of lactose, vitamin D, increase of salivary cortisol	2+	C

Abbreviations: AA, amino acids; ASD, autism spectrum disorder; CF, casein-free diet; FFQ: Food frequency questionnaire; GF, gluten-free diet; GFCF, gluten-free, casein-free diet; GR, grade of recommendation; LE, level of evidence; RCT: randomized clinical trial.

^aThe studies classified as 1- and 2- were not used for establishing the recommendations given their high risk of bias.

treatments provided, or the use of 1 or more intervention procedures that could affect the assessment criteria selected.

For evaluating and synthesizing the scientific evidence, we also considered the internal validity of the studies, whether there was statistical significance and the accuracy of the results, as well as their clinical relevance. We then characterized the recommendations on the basis of the quantity, generality, and clinical relevance of the results as well as the quality of the scientific evidence.

Results

The studies retrieved were analyzed in terms of the following characteristics, as applicable: sample size, study design, assessment and intervention criteria, and the results, as well as the level of evidence and the grade of recommendation. Tables 3 and 4 summarize the characteristics of the studies, the results of which have been referred to above.

Effectiveness

Scientific literature on this topic is relatively scarce. Among the studies that refer to effectiveness, only four^{12,34,35,56} can be considered to provide high scientific evidence. The studies of Harland⁵⁷ and Hyman⁵⁸ are not yet completed. Millward⁵⁹ and Mulloy^{60,61} present systematic reviews evaluated with the highest level of evidence and grade of recommendation. Notably, in our analysis, the studies that reported positive results were classified with the lowest levels of evidence, whereas the rest reported negative results with regards to this type of dietary intervention. None of the studies identified provided conclusive evidence because they had poor validity (Table 3).

Safety

There are similarly few publications addressing the safety of the gluten-free, casein-free diet. Among those identified, the studies of Konstantynowicz et al⁴⁶ and Hediger et al⁵⁰ provide the highest level of evidence. Nevertheless, in the results found, there was a certain degree of consensus on the risks that could be associated with following this type of restriction diet (Table 4).

Discussion

Data in the literature in this field are very limited both in quantity and quality. To assess the effectiveness and safety of the gluten-free, casein-free elimination diet, we considered both behavioral (verbal and nonverbal communication, stereotypy, and disruptive behavior) and biomedical variables (eg, urinary peptides, gliadin and endomysial antibodies, as well as other laboratory data and nutrient intake). Methodologic limitations identified were associated with a range of factors: the lack of a control group and/or clear definitions of inclusion criteria, very small sample sizes, and analysis being based on single individuals or anecdotal information, groups being heterogeneous in terms of age, failure to control for phenotypic variability between individuals, interventions being of variable duration and generally short, as well as lack of preintervention-

postintervention comparisons. There was also a risk of bias in data on the behavioral variables attributable to memories of parents and other caregivers being distorted over time and that their perception of changes in the behavior of participants can be subjectively influenced by the fact of being included in non-blinded trials. Similarly, a placebo effect could have had an impact on the results. Lastly, alternative explanations were not always considered, such as the risk of confounding bias, in particular, it being possible that behavioral improvements were due to ongoing development and behavioral therapy given, rather than to gluten-free, casein-free diets per se. Finally, it should be noted that the literature search cannot have identified all the relevant publications, and the review itself can be sensitive to information bias.

Recommendations

On the basis of this review, we conclude that the evidence to support gluten-free, casein-free diets is limited and weak, such dietary restrictions being associated with social rejection, stigmatization, deficits in socialization and integration, and a misuse of resources, as well as potential adverse biomedical effects. Hence, we advise against resorting to elimination diets in an attempt to treat autism spectrum disorders. Specifically, until there is conclusive evidence of the benefits of gluten-free, casein-free diets in autism spectrum disorders, they should only be introduced after the diagnosis of an intolerance or allergy to allergens in the foods that would be eliminated in such a diet. Similarly, the results retrieved do not support the opioid theory.

Implications for the Practice

As a final recommendation, we underline that, when used, elimination diets must be at least as closely monitored as other types of intervention, to allow doctors, parents, and other caregivers to optimize treatments and hence health outcomes for these children. On the other hand, a diet-related specific end phenotype can be a target for future research and even a marker for the gluten-free, casein-free dietary intervention.

Based on the results of this review, future research should be focussed on blinded randomized controlled trials, and include larger samples sizes.

Author Contributions

All 5 coauthors of this paper have contributed significantly to the design and implementation of the study, as well as the analysis and interpretation of the results. Further, all have participated in the preparation of this manuscript and have approved the final version submitted for publication.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study protocol was approved by the Ethics Committee of the University Hospital "Dr. Peset" (Valencia, Spain) (code 46/10). The school accepted the study, and parents of the children participating in the study gave written informed consent.

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