Review Paper

The Use of Dietary Interventions in Pediatric Patients

Shirin Madzhidova [1], and Lusine Sedrakyan [2]

[1] Assistant Professor, PCOM School of Pharmacy Georgia Campus; shirinma@pcom.edu
[2] Doctor of Dental Medicine, Byrd Dental Group; lusinesedrakyan91@gmail.com
* Correspondence: shirinma@pcom.edu; Tel.: 678-407-7333

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Abstract: Complementary and alternative treatment approaches are becoming more common among children with chronic conditions. The pravelance of CAM use among US adults was estimated to be around 42% in 2015, and around 44% to 50% among adults with neurologic disorders. Studies report children with chronic illnesses such as cancer, asthma, attention-deficit/hyperactivity disorder (ADHD), genetic disorders, and other neurodevelopmental disorders are treated with complementary and alternative treatments at higher rates. Dietary therapies are gaining increasing popularity in the mainstream population, due to the heavy media involvement. Although, majority of "fad" diets do not have enough supporting evidence, some dietary therapies have been utilized for decades and have numerous published studies. The objective of this review is to describe the dietary interventions used in children with the specific chronic conditions, to evaluate their efficacy based on published data, and to encourage pharmacist involvement in the management and care of such patients.

Keywords: pediatric pharmacy; complementary alternative medicine; dietary interventions; oral manifestations; chronic pediatric conditions; ketogenic diet; gluten free casein free diet

Introduction

Complementary and alternative treatment approaches are becoming more common among children with chronic conditions. The National Center for Complementary and Alternative Medicine at the National Institute of Health (NIH) groups complementary and alternative medicine (CAM) into broad categories such as whole medical systems, mind-body medicine, biologically-based therapies, manipulative and body-based practices and energy medicine.1 The pravelance of CAM use among US adults was estimated to be around 42% in 2015, and around 44% to 50% among adults with neurologic disorders.2, 3 Studies report children with chronic illnesses such as cancer, asthma, attention-deficit/hyperactivity disorder (ADHD), genetic disorders, and other neurodevelopmental disorders are treated with complementary and alternative treatments at higher rates (24%-75%).4-7 Among those, supplement and herbal medications, as well as dietary modifications (i.e., elimination or intake of specific foods) are most prevalently used at 31% and 17% respectively. Parents of children with conditions that lack effective medical approaches or complete remissions often turn to alternative treatment approaches with the notion that they are generally risk-free. A survey of parents found that more than 50% had used at least on type of CAM therapy for their children with ASD, which is not always reported to the health-care provider. 8, 9. Dietary therapies are gaining increasing popularity in the mainstream population, due to the heavy media involvement. Although, majority of "fad" diets do not have enough supporting evidence, some dietary therapies have been utilized for decades and have numerous published studies. Nevertheless, CAM approaches, such as dietary interventions, pose potential challenges when integrated with conventional treatments as well as with the risk of adverse effects. For those patients who are undergoing integrative treatment, close collaborative management from the health-care provides is essential in ensuring the success of the treatment and the health of the patient.

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Ketogenic Diet for Epilepsy

Epilepsy is a group of neurologic disorders characterized by episodes of recurring seizures, the cause of which is mostly unknown. Despite continued advancements in anticonvulsant pharmacotherapy, 30% of patients with epilepsy have refractory seizures unresponsive to pharmacologic treatment or experience intolerable side effects from medications.10 The ketogenic diet (KD) is a non-pharmacologic treatment for children with refractory seizures that has been used worldwide for decades. The Ketogenic Diet Study Group, a panel comprised of 26 pediatric specialists and dieticians, published a consensus report agreeing the KD should be strongly considered in a child who failed two to three anticonvulsant therapies, particularly in those patients with symptomatic generalized epilepsies.11

Fasting has been utilized since the 1920's to alleviate symptoms of seizures, although the exact mechanism was not yet known. It was believed that an intoxication of the brain from substances in the intestines was the main cause of epilepsy and fasting was reported to have high rates of efficacy.12 It was later reported that ketone bodies caused by starvation were responsible for the anticonvulsant effect, and can be produced as a result of oxidation of certain acids in the absence of sufficient glucose. The ketogenic diet (KD) for the treatment of epilepsy has first been reported in 1921 and had been studied extensively since.13 The diet consists of mainly fat and protein consumption, with very low intake of carbohydrates (e.g., 4:1, 3:1, 2:1 ratio). Energy consumption mainly from fat is thought to mimic a state of ketosis.

Although not completely understood, several theories exist regarding the mechanism of action of KD. It has been proposed that utilization of ketones for energy metabolism in the brain results in adaptive changes which increase energy reserves and gamma-aminobutyric acid (GABA) synthesis (major inhibitory neurotransmitter), resulting in seizure resistance. Ketone bodies themselves are thought to possess anticonvulsant properties since they are structurally similar to GABA, betahydroxybutyrate, and acetoacetate. The diet also has been documented to be neuroprotective by inhibition of caspase-3-mediated apoptosis and through the activation of mitochondrial uncoupling proteins, which can reduce the production of reactive oxygen species.14

The ketogenic diet encompasses various modalities of implementation, however, the majority of clinical data available are for the classic KD, which consists of 85-90% caloric intake from long-chain triglycerides in a 4:1 ratio of fat to non-fat sources. The classic KD is recommended for children however, a 3:1 ratio for adolescents and a 2:1 ratio for infants may be used since more protein is required in these age groups. The diet is further modified to allow for appropriate growth and development of a child. Initiation of the KD most often occurs in an acute care setting at an epilepsy center in order to safely monitor ketone and glucose levels, with an average hospital stay of four days. The diet is traditionally introduced slowly following a 24-48 hour fasting period, until the patient tolerates full KD and is then discharged home.

Efficacy of the KD on seizure activity in published studies varies, although the majority of studies show some reduction in seizure occurrence. A meta-analysis of 19 observational studies (1084 patients) found approximately 60% of patients had a greater than 50% seizure reduction and 30% had greater than 90% seizure reduction six months after initiation of a KD.15 A randomized controlled trial including 145 children found the mean percentage of baseline seizures was lower in the KD

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group at 3 months, compared to the control group who had experience an increase in seizures from baseline (62% versus 137%; P < 0.0001).16

Variations of the KD exist, although the most commonly prescribed are the classic KD, the medium-chain triglyceride (MCT) diet, the modified MCT diet, the modified Atkins diet, and the low-glycemic index treatment diet. The MCT diet is comprised of 71% medium-chain fatty acids, 10% protein, and 19% carbohydrates. The MCT diet uses fat sources that are more ketogenic than the long-chain triglycerides (LCT) utilized in the classic KD, therefore allowing for less fat consumption and more protein and carbohydrates to be incorporated into diet. Alternatively, the modified MCT diet combines the use of LCT (40-50% of calories) and MCT (30% of calories), as well as protein (10-20%), and carbohydrates (5-10%). A trial comparing the MCT diet, classic LCT diet, as well as a modification of the 2, found they were of roughly equal efficacy, with a higher incidence of gastrointestinal irritation with the MCT diet.17

Variations of the KD, including the modified Atkins diet and low-glycemic-index treatment both can utilize medium-chain or long-chain triglycerides (65% calories from fat), with a larger daily allowance of carbohydrate intake, which offers more flexibility in meal preparation to the caregiver. These diets can be initiated in an outpatient setting.18 A study of 20 patients with retractable epilepsy on an Atkins diet, showed greater than 50% reduction in seizures at 6 months in the majority of patients. These results closely correlate to the efficacy of the classic KD.19

Although, generally considered to be a safe treatment choice, KD has been shown to cause several adverse events in children and adults. During initiation of the diet, acidosis, dehydration, hypoglycemia, and gastrointestinal distress have been reported as the most prominent adverse events but are typically transient and easily managed. Other reported adverse events associated with KD maintenance include poor growth, nephrolithiasis, dyslipidemia, prolongation of QT interval, cardiomyopathy, excessive bruising, vitamin D deficiency, trace mineral deficiencies, constipation, and exacerbation of gastrointestinal reflux disease.20Cholesterol and lipids have been shown to be adversely affected, with a reported increase of total cholesterol of ~ 130%, which then stabilized over 2 years.20 Certain conditions, such as the history of kidney stones, dyslipidemia, liver disease, gastroesophageal reflux disease, constipation, cardiomyopathy, or metabolic acidosis, may be aggravated by the diet and require close monitoring and testing.20

Serious complications associated with the KD appear to be relatively rare, while the long-term complications are not well documented. Overall, the KD is an effective treatment for epilepsy in children, and as with any other medical treatments, requires individualized care, close monitoring, and follow-up by the health-care provider.21

Pharmacists can play an important role in management of patients on the KD and concomitant pharmacologic therapy. Many medications, specifically pediatric liquid preparations, have a high carbohydrate content, which may compromise ketosis. Carbamazepine suspension, ethosuximide syrup, phenobarbital elixir, and valproic acid syrup contain the highest amounts of carbohydrates and should be avoided in ketogenic diet patients.22 Alternatively, these patients may be given the capsule or crushed tablet formulation, which generally contain very low amounts of carbohydrates. Despite a long history of combined use of anticonvulsants and the KD, it remains unclear whether there are negative or positive pharmacodynamic interactions, and only scant information regarding the impact of KD on the pharmacokinetics of anticonvulsants. Abnormal laboratory parameters may be seen in children on KD; however, metabolic acidosis requiring treatment may be more common with concomitant use of topiramate or zonisamide, particularly at the initiation of KD. It is recommended that bicarbonate concentrations should be monitored carefully, especially when receiving these anticonvulsants, and that bicarbonate supplements be given only when patients are clinically symptomatic (e.g., vomiting, lethargy).20

Gluten-free Casein-free Diet for Autism Spectrum Disorder

Prevalence of autism and autism spectrum disorder (ASD) has been on the rise, and most recently reported to occur in 1 in 88 children in the United States.23 According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, autism is characterized by qualitative impairments in social interaction and communication, as well as restrictive, repetitive, and stereotyped patterns of behavior, interest and activity. In the most recent edition of the manual, previously distinct autism subtypes, including autistic disorder and Asperger syndrome, are now collapsed into one unified diagnosis of autism spectrum disorder (ASD).24, 25

Definitive etiology of ASD is not yet clearly understood since several studies attribute the disorder to genetic factors, metabolic derangements, and environmental or dietary causes.26 Gastrointestinal issues, such as chronic constipation or diarrhea, are among the most common medical conditions associated with autism, although a direct correlation has not been substantiated. A study comparing GI problems in children with autism and children with other neurodevelopmental disorders such as cerebral palsy, reported that 70% of children with autism were affected compared with 42% of children with other neurodevelopmental disorders and 28% of children with normal development.27 In a study conducted by Campbell et al, 9% of unaffected siblings of children with ASD had a gastrointestinal disorder whereas the prevalence in children with autism was 41% (P=0.000).28 Considering the proposed etiology of GI involvement in ASD, many research articles have been published looking at dietary interventions to alleviate symptoms in children with ASD.

Specific dietary interventions in children with ASD include the omission of gluten and casein containing foods. Gluten is a protein found in wheat, rye, and barley whereas casein is the main protein in dairy products. The cessation of gluten and casein is based on the theory that opioid peptides, formed from the incomplete breakdown of foods containing gluten and casein, may enter the bloodstream due to increased intestinal permeability, cross the blood-brain barrier and affect central nervous system development and functioning.29 Therefore, avoidance of foods containing gluten and casein is suggested to alleviate behavioral symptoms associated with ASD. Although widely reported and used, the diet and its proposed etiology lacks substantial evidence for efficacy, with only a few well-designed trials published. The prevalence of use of the gluten-free and casein-free diet among children with ASD is estimated at 40%.30

Although anecdotal reports from parents of success with the diet flood online forums, scientific evidence for its effectiveness remains inconclusive. A systematic review conducted in 2008 summarized two randomized controlled trials evaluating gluten-free casein-free (GFCF) diets in children with ASD. While one of the studies concluded the GFCF diet significantly reduced the severity of autistic symptomatology, the other study found no difference in the outcomes.31 A recent randomized-controlled trial evaluated children with ASD randomly allocated to a GFCF diet or a low sugar diet for 3 months using an open-label design. While improvements in a range of behavioral and developmental outcomes were observed among both groups, there were no statistically significant differences between the groups.32 A study published in 2013 utilized research synthesis technique to review major articles published on the use of GFCF diet in children with ASD.33 In their assessment the authors identified most studies did not support the use of the GFCF diet in ASD and presented various limitations in the study design of the trials. Additionally, they noted most studies incorporated GFCF with other treatment modalities making it difficult to assess the effectiveness of GFCF alone, and subpopulations including Rett Syndrome and Childhood Disintegrative Disorder (CDD) require further studies to determine efficacy. Overall, the American Academy of Pediatrics does not recommend the use of GFCF for ASD due to the lack of sufficient evidence, while the United Kingdom 2013 National Institute for Health and Care Excellence (NICE) clinical guideline on the management of ASD suggests the potential risks of GFCF outweigh their benefits.34

The majority of studies on GFCF did not report any serious adverse effects from the diet. However, an observational study on the provision of GFCF suggests casein restriction may lead to decreased bone mass and essential amino acid deficiency, such as tryptophan. It is important for health-care providers to counsel families on the need for adequate vitamin D, calcium, and protein supplementation, since most milk substitutes do not contain appropriate amounts of protein. Another potential harm of adopting a GFCF diet is the potential to overlook possible underlying celiac disease or lactose intolerance. Celiac disease is the most common autoimmune gastrointestinal disorder for which the treatment is complete avoidance of gluten.35 Pharmacist need to be aware of medications that may contain gluten as an excipient and recommend alternative agents for patients with celiac disease or on a GFCF/gluten-free diet.

Specific Carbohydrate Diet (FODMAPs) for Crohn's Disease

Functional gastrointestinal disorder (FGID) is defined by the Rome III criteria as a variable combination of chronic or recurrent gastrointestinal symptoms such as diarrhea, constipation and abdominal pain, which are not explained by structural or biochemical abnormalities.36 Types of FGID include irritable bowel syndrome (IBS), functional abdominal pain, functional dyspepsia and abdominal migraine, with IBS being the most common. The etiology of FGID is poorly understood however; food intolerance such as malabsorption of carbohydrates has been implicated in the pathogenesis of FGID with recently emerging studies. Most symptoms of irritable bowel syndrome (IBS) are due to luminal distension of the distal small and proximal large intestine, causing pain, bloating, and abdominal distension. Solid, liquid or gas materials present in the gut can promote the distension of the lumen. Solids, mostly in the form of fiber, can either expand or contract the bacterial mass of the gut. Liquids, may dictate the osmotic absorption or retention in the lumen. While gas can be ingested in the form of excess nitrogen, but is mostly produced by bacterial fermentation. Therefore, dietary components that may lead to these changes in the lumen of the intestine are generally poorly absorbed, are small molecules, and can be readily fermented by bacteria. Dietary fermentable Oligo-, Di- and Monosaccharides and Polyols (FODMAPs) are the best fit for such molecules.

Fermentable Oligo-, Di- and Monosaccharides and Polyols (FODMAPs), are short-chain carbohydrates and sugar alcohols (polyols), which comprise fructose, lactose, fructo- and galactooligosaccharides (i.e., fructans, galactans), and polyols (e.g., sorbitol, mannitol, xylitol, maltitol). These dietary components have three common properties; they are poorly absorbed in the small intestine, they are small and osmotically-active molecules, and they are rapidly fermented by bacteria. All of these properties can potentially contribute to the exacerbation of FGID symptoms. A low-FODMAP diet alleviates gastrointestinal symptoms by reducing the amount of undigested carbohydrates that presents to colonic bacteria, leading to less fermentation, resulting in decreased abdominal bloating and pain as well as flatulence.

Initial studies in adults have demonstrated significant improvement of IBS symptoms in patients on the low FODMAP diet. In a randomized, single blind, crossover trial, 30 patients with IBS and 8 healthy patients were put on a low or moderate FODMAP diet for 21 days. Adult patients with IBS had significantly improved satisfaction with stool consistency and decreased abdominal pain, bloating, and flatulence, when on the low FODMAP diet.37 Limited studies exist however, for the use of low FODMAP diet in children with IBS. Two studies, with limited power, studied the effects of fructose on the GI tract and elimination of fructose in children with fructose malabsorption. The studies indicated that administration of fructose produced a positive hydrogen breath test in 11 out of 32 children and fructose elimination was effective in reducing functional abdominal pain symptoms in 77% of studied children.38, 39 In a double-blind randomized controlled trial of 54 children with IBS, a low-FODMAP diet was compared to a high-FODMAP diet using crossover design. The authors found fewer episodes of abdominal pain, less bloating, less nausea and lower breath hydrogen production after only 2 days on the low-FODMAP diet.40 Further studies in

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children are needed to confirm the efficacy of the low-FODMAP diet for IBS and to determine its value in other forms of FGID.

Although limited, reports regarding the safety of the FODMAPs diet indicate certain risks exist. Due to the lack of ingestion of foods that are considered prebiotics, the gut microflora may be diminished, which could potentially be detrimental to large bowel health (e.g., promotion of colorectal carcinogenesis). The lack of fiber intake could arise from restricted intake of wheat-containing foods. In adolescents, the possibility of eating disorders comes into play, as a result of the innate possibility of IBS or food restrictions with the diet.41 Close monitoring and counseling by a dietician is essential to ensure compliance and positive outcomes with the diet. For the patients who are on the diet, it is important for health-care providers to consider the presence of fructose or lactose in some pediatric drug formulations that may potentially worsen symptoms.

Although the GI tract is the primary site of involvement in CD, many cases, particularly in pediatric patients, first present with non-intestinal manifestations, including oral lesions.42 Younger pediatric patients often also present with weight loss, delayed growth, or failure to thrive.43

Studies have shown that oral manifestations of CD in children occur in around 50%-80% of cases, and about 30% of CD cases in children occur first in the mouth.44 One study suggested as high as 60% of cases of pediatric CD have oral symptoms as the first presenting sign of the disease.45 Oral lesions can precede, occur concurrently, or follow the onset of abdominal symptoms, although synchronous observation is most commonly described. Failure to include IBD, particularly CD, on the differential for oral manifestations can lead to delay in diagnosis and treatment for patients or extensive unnecessary workups.46

The most common sites for clinical presentation of oral lesions in CD are the lips, gingiva, vestibular sulci and buccal mucosa.45 Mucogingivitis occurs in about 25% of cases, followed by multiple and persistent superficial oral ulcers simulating minor aphthous ulcers, which occur in about 8% of the cases.47 Cobblestone papules of the buccal mucosa and vestibule occur in about 6% of the patients.48 These findings may be associated with pain, impairment of oral function, and psychosocial stress.45 Other non-specific oral findings of CD include angular cheilitis, persistent submandibular lymphadenopathy, gingivitis, and periodontal disease.49, 50

While the exact causes of Crohn's disease remain unknown, some studies have postulated that changes in the immune system and exposure to environmental risk factors, including responses to gastrointestinal bacteria, may be triggers of CD.51 Dysregulation of various components of the immune system can be seen in the gut of patients with CD. This dysregulation is thought to be sustained by increased local proinflammatory cytokine products and by defects in counter-regulatory mechanisms.52 Recognizing oral lesions in the pediatric population and requesting a biopsy of the accessible papules and/or the superficial ulcers may help expedite the diagnosis of CD.

Dietary Interventions for ADHD

Attention deficit hyperactivity disorder (ADHD) is a common disorder in children of school years. According to the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth edition (DSM-5), ADHD is characterized by symptoms of inattention, overactivity, and/or impulsiveness that are age inappropriate, persistent, and pervasive.53, 54

ADHD is associated with a significant risk of educational failure, interpersonal problems, mental illness and delinquency, a substantial burden on families, as well as on health, social care, and criminal justice system, in the long run.55

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Generally, pharmacologic treatments for management of ADHD are preferred and widely used; however, a multimodal approach to treatment is recommended. A variety of non-pharmacologic and dietary interventions for the management of ADHD have been studied with mixed results. One of the earliest studied dietary interventions for ADHD was the Feingold diet, which was introduced in the 1970's by Dr. Feingold who believed certain additives in food were associated with hyperactivity. Foods avoided on the Feingold diet include apples, grapes, luncheon meats, sausage, hot dogs, and drinks containing artificial flavors and coloring agents. Products containing red and orange synthetic dyes, as well as preservatives, butylated hydroxytoluene and butylated hydroxyanisole were advised against.56 The diet gained popularity when initially introduced among physicians and was claimed to ameliorate symptoms in more than 50% of children treated for hyperactivity. Several controlled studies performed since failed to show the same efficacy, however a small subgroup of children that may be susceptible have been identified.57 More recent versions of the diet recommend avoiding artificial food coloring and additives only.58

A meta-analysis published in 2012 evaluated studies on restriction diets for ADHD, in particular elimination of food colors. From the 34 high-quality studies selected, the authors were able to report that while parent reports yielded statistically significant reduction in symptoms among patients who eliminated food dyes, teacher/observer reports yielded no significant effect. This illustrates the concept of observer bias, since parents are more likely to think an intervention is helping their child, therefore influencing the results. The authors concluded that an estimated 8% of children with ADHD may have symptoms related to synthetic food dyes, and that further studies are warranted.59

Another commonly used dietary intervention for children with ADHD is an oligoantigenic (hypoallergenic/elimination) diet. Oligoantigenic diet eliminates most known sensitizing food antigens or allergens, such as cow's milk, cheese, wheat cereals, egg, chocolate, nuts, and citrus fruit, in an attempt to identify and treat food allergies and intolerances that may be linked to neurologic dysfunction. More recently known as "elimination diet", these diets may vary in their specific contents. A multi-food exclusion diet, such as the 6-food elimination diet, eliminates most common food allergens. A "few foods diet" restricts a person's diet to a few less consumed foods with low antigenic potential, such as lamb/venison, quinoa/rice, pear, and others. Individuals on a "few foods diet" must be closely monitored by a dietician to avoid nutritional deficiencies.60 Most elimination diets follow a 2-step process, where the diet is followed for a period of time, then foods are reintroduced one at a time to identify those that are causing symptoms.

Two recent meta-analyses were conducted to evaluate the diet effects of both restriction/elimination diets and food colorings on ADHD. The authors concluded that the diet effect on children with ADHD, particularly those with severe symptoms, may be larger than those without ADHD, and that elimination diets might work. However, both meta-analyses noted the questionable study methods in most evaluated studies, as well as the difficulty in generalizing of symptom improvement.59, 61

Overall, data on the effectiveness of elimination diets are conflicting and requires additional, well-designed, studies with a large sample size. For those parents of children with ADHD who do choose to implement elimination diets in their treatment regimen, pharmacists are able to assist with proper selection of medication excipients. Many liquid pediatric formulations contain food dyes as well as certain FODMAPs. By identifying the origin of the excipient in the prescribed or over-the-counter medications these children may be taking, pharmacists can help patients to avoid those triggers and maintain their diet regimen. A summative list of common medication excipients is provided in the table below.

Conclusion

Neurodevelopmental disorders are complex in nature, whose pathophysiology is not yet completely understood. Due to the challenges with selection of appropriate pharmacologic management,

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326 complementary and alternative treatment modilities are becoming more common among pediatric
327 patients. Many parents feel that dietary interventions are a safe alternative, especially in the cases of
328 conventional treatment failure. Although, generally considered safe, dietary interventions do pose
329 certain risks and require proper management. Pharmacists can play an important role in providing
330 helpful information to parents of children with such disorders, in both managing their diets and
331 preventing adverse effects. Communication with patients continues to prove its importance in many
332 facets of pharmacotherapeutic management, but is ever more valuable for those patients also utilizing
333 alternative therapies. Majority of the dietary interventions mentioned in this article do not have
334 enough evidence to support use as monotherapy. Larger and better structured studies are necessary
335 to further identify their place in management of neurodevelopmental disorders.
336

Common Medication Excipients that May Contain Gluten[1,2]		
Excipient	***Gluten-free botanical source***	***Gluten Containing botanical source***
Starch	Corn, potato, tapioca	Wheat
Pregelatinized starch, pregelatinized modified starch, sodium starch glycolate	Corn, rice, potato	Wheat
Dextrans	Corn, potato	Wheat, barley
Dextrose	Corn	Wheat, barley
Dextrates, dextrins	Corn, potato	Wheat, barley
Maltodextrin	Corn, potato	Wheat, barley
Caramel coloring		Barley malt
Resources for more information about gluten in medications[3]		
List of medications verified to be gluten-free		*www.glutenfreedrugs.com*
"A guide through the Medicine Cabinet" (book)		*In print*
Walgreens and CVS pharmacy OTC brand medication list		*Available upon request*
Additional information on gluten in foods and products		*www.celiac.org* *www.celiaccentral.org*
FODMAP Carbohydrate Food Sources (to be avoided)[4]		
Fructo-oligosaccharides (fructans)	Wheat, rye, onions, garlic, artichokes	
Galacto-oligosaccharides (GOS)	Legumes	
Lactose	Milk and milk products	
Fructose	Honey, apples, pears, watermelon, mango	
Sorbitol	Apples, pears, stone fruits, sugar-free mints/gums	
Mannitol	Mushrooms, cauliflower, sugar-free mints/gums	
Common pediatric medications with high carbohydrate content (≥2 grams/dose)[5] *		
		Dosage unit

Acetaminophen liquid suspension (cherry) (Tylenol)	160 mg/5mL
Acetaminophen elixir with codeine (Tylenol with Codeine) *0.35 g ethyl alcohol/5mL	120 mg/5mL
Amoxicillin oral suspension (Trimox)	125 mg/5mL
Ampicillin oral suspension (Omnipen)	125 mg/5mL
Carbamazepine suspension (TEGretol)	100 mg/5mL
Cephalexin oral suspension (Keflex)	125 mg/5mL
Phenobarbital elixir *0.71 g ethyl alcohol/5mL	20 mg/5mL
Valproic acid syrup (Depakene)	250 mg/5mL

* For a more comprehensive list of medications refer to article reference (5)

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