

# Natural Approaches to Epilepsy

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## Abstract

This article reviews research on the use of diet, nutritional supplements, and hormones in the treatment of epilepsy. Potentially beneficial dietary interventions include identifying and treating blood glucose dysregulation, identifying and avoiding allergenic foods, and avoiding suspected triggering agents such as alcohol, aspartame, and monosodium glutamate. The ketogenic diet may be considered for severe, treatment-resistant cases. The Atkins diet (very low in carbohydrates) is a less restrictive type of ketogenic diet that may be effective in some cases. Nutrients that may reduce seizure frequency include vitamin B6, magnesium, vitamin E, manganese, taurine, dimethylglycine, and omega-3 fatty acids. Administration of thiamine may improve cognitive function in patients with epilepsy. Supplementation with folic acid, vitamin B6, biotin, vitamin D, and L-carnitine may be needed to prevent or treat deficiencies resulting from the use of anticonvulsant drugs. Vitamin K1 has been recommended near the end of pregnancy for women taking anticonvulsants. Melatonin may reduce seizure frequency in some cases, and progesterone may be useful for women with cyclic exacerbations of seizures. In most cases, nutritional therapy is not a substitute for anticonvulsant medications. However, in selected cases, depending on the effectiveness of the interventions, dosage reductions or discontinuation of medications may be possible. (*Altern Med Rev* 2007;12(1):9-24)

## Introduction

Epilepsy is a disorder of brain electrical activity that results in recurrent seizures. The type of seizure depends on the portion of the brain affected. While there are many different causes of seizures, including brain tumor, head injury, stroke, and alcohol withdrawal, the discussion in this article is limited mainly to cases in which the cause is idiopathic (primary epilepsy).

Conventional treatment of epilepsy consists primarily of anticonvulsant medications. Although these drugs often control or reduce the frequency of seizures, some patients show little or no improvement.

A number of dietary modifications, nutritional supplements, and hormones have been found to be beneficial for some patients with epilepsy.

Potentially useful dietary interventions include measures to stabilize blood glucose levels, identification and avoidance of allergenic foods, and avoidance of potential inciting agents (such as ethanol and aspartame). The ketogenic diet has been successful for many patients, but because of its highly restrictive nature and potential to cause significant adverse effects, its use is restricted to severe cases that fail to respond to other treatments. A less restrictive version of the ketogenic diet, the Atkins diet, has shown promise and deserves further study.

Several different nutrients (and two hormones) may also be beneficial in selected patients with epilepsy. The fact that nutritional factors are involved in the regulation of electrical activity in the brain is indicated

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by the fact that severe deficiency of thiamine, magnesium, or vitamin B6 can cause seizures. A subnormal concentration of each of these nutrients has been found to be common in patients with epilepsy. While the severity of these deficiencies is probably not great enough in most cases to cause seizures in otherwise healthy people, marginal status with respect to any of these nutrients could conceivably exacerbate a seizure disorder due to another cause.

In addition, some patients with epilepsy might have a higher-than-normal requirement for one or more nutrients that play a role in brain electrical activity. That phenomenon has been clearly demonstrated in the case of vitamin B6-dependent epilepsy, a condition in which intractable seizures can be completely controlled by administration of large doses of vitamin B6. The existence of this relatively rare syndrome raises the possibility that more subtle forms of nutrient dependency occur more commonly. While mildly or moderately increased requirements for vitamin B6 or other nutrients may not by themselves be sufficient to cause seizures, a failure to meet these increased requirements could aggravate an existing seizure disorder.

Some studies have found that supplementation with individual nutrients reduced seizure frequency or improved other aspects of health in patients with epilepsy, but other studies have failed to confirm those findings. Administration of combinations of nutrients might be more effective than supplementing with a single nutrient, but that possibility has largely been unexplored. Nutrient supplementation may also be necessary to prevent or reverse the effects of certain deficiencies that frequently result from the use of anticonvulsant drugs. The potential benefits of nutrient supplementation in patients with epilepsy must be weighed against reports that large doses of certain nutrients (such as vitamin B6 and folic acid) can interfere with the effects of anticonvulsants.

Because there are many different types of epilepsy, a nutritional intervention that is helpful for one patient may not be beneficial for another. Some studies did not specify the types of epilepsy being treated, so it is difficult to generalize results. Nevertheless, natural approaches to the treatment of epilepsy show promise and should be considered as part of the overall treatment of epilepsy.

## Dietary Factors

### *Hypoglycemia/Hyperinsulinemia*

Seizures are a known manifestation of hypoglycemia.<sup>1,2</sup> In patients with epilepsy, hypoglycemia might decrease the threshold for seizure development. In one study of 92 patients with epilepsy, 56.4 percent were found to have a subnormal fasting blood glucose concentration.<sup>3</sup>

In addition, transient EEG abnormalities have been observed in some patients during a glucose tolerance test. These abnormalities occurred, not when the blood glucose level was at its lowest point, but at a time that insulin levels would have been expected to be elevated.<sup>4</sup> These EEG changes were hypothesized to result from insulin-induced transport of water and electrolytes into the brain, leading to cerebral hyperosmolality. While the observed EEG changes were not necessarily of the type associated with seizures, these findings raise the possibility that hyperinsulinemia could trigger seizures in patients with epilepsy.

Thus, hypoglycemia and hyperinsulinemia might each contribute to the pathogenesis of epilepsy in some cases. Patients with epilepsy who have evidence of these abnormalities might benefit from nutritional interventions, such as avoiding refined sugar, caffeine, and alcohol; eating frequently; consuming adequate amounts of protein; and supplementing with chromium, other trace minerals, magnesium, and B vitamins.

### *Food Allergy*

In case reports, specific foods were implicated in epilepsy causation;<sup>5</sup> the avoidance of symptom-evoking foods resulted in a reduction in seizure frequency or elimination of seizures.<sup>6,7</sup> In a study of 63 children with epilepsy, identification and avoidance of allergenic foods was frequently successful for patients who had other symptoms suggestive of allergy, but not for children who had epilepsy alone.

For four weeks, 63 children with epilepsy underwent an elimination diet consisting of lamb, chicken, potato, rice, banana, apple, cabbage, sprouts, cauliflower, broccoli, cucumber, celery, carrots, parsnips, water, salt, pepper, pure herbs, calcium, and vitamins. Of 18 children who had epilepsy alone, none improved. The other 45 children with epilepsy also had recurrent migraines, abdominal symptoms, or hyperkinetic behavior. Of



## Review Article

those children, 55.6 percent stopped having seizures and an additional 24.4 percent had fewer seizures during diet therapy (a total of 80 percent with complete or partial resolution of seizures). Headaches, abdominal pains, and hyperkinetic behavior resolved in all patients whose seizures resolved, as well as in some patients who continued to have seizures. Symptoms were evoked by 42 different foods, and seizures occurred after ingestion of 31 different foods. Most children reacted to several foods. Both generalized epilepsy (including myoclonic seizures and petit mal) and partial epilepsy improved on the diet. In double-blind, placebo-controlled food challenges, symptoms recurred in 15 of 16 children, including seizures in eight cases, after ingestion of offending foods; whereas, no symptoms recurred when placebo was given.<sup>8</sup>

The prevalence of celiac disease has been found to be higher in patients with epilepsy than in controls (1/44 versus 1/244, respectively).<sup>9</sup> Seizures have improved in patients with celiac disease who consumed a gluten-free diet,<sup>10</sup> but only when the diet was started soon after the onset of epilepsy.<sup>11</sup> Most epileptic patients with celiac disease did not have gastrointestinal symptoms at the time of presentation, so testing for celiac disease should be considered even in the absence of such symptoms. Some patients with epilepsy and celiac disease have also been found to have cerebral calcifications,<sup>12-14</sup> the significance of which is not clear.

### **Dietary Inciting Factors**

In some cases, epileptic seizures have been triggered by excessive alcohol intake.<sup>15</sup>

Two case reports indicate ingestion of monosodium glutamate appeared to trigger or exacerbate seizures in children.<sup>16</sup>

Grand mal seizures have occurred after consumption of aspartame by people who had no prior history of epilepsy.<sup>17,18</sup> Ingestion of a drink containing aspartame (40 mg/kg body weight) also exacerbated EEG spike-wave discharges in children with a history of absence seizures.<sup>19</sup>

However, in trials funded by the NutraSweet Company (the manufacturer of aspartame), administration of aspartame (34 mg/kg/day for two weeks or a single dose of 50 mg/kg) did not provoke seizures in patients with epilepsy or in people who reported a history

of aspartame-induced seizures.<sup>20,21</sup> A potential limitation of these trials is that aspartame was administered in capsules, rather than in soft drinks or other aspartame-containing foods or beverages. As aspartame in commercial products is said to undergo chemical changes on exposure to high temperatures or after storage for more than two months, these degradation products may be partly responsible for the reported adverse effects of aspartame.<sup>22</sup> Therefore, symptoms that occur after ingestion of aspartame-containing commercial products or hot drinks to which aspartame has been added may not be reproducible by challenging with aspartame in capsules. Based on the available evidence, aspartame should be considered a potential trigger for seizures and should be excluded during an elimination diet.

### **Ketogenic Diet**

The ketogenic diet has been used since 1921 to control seizures in children who do not respond to anticonvulsant medications.<sup>23-31</sup> The diet is calorie-restricted and provides a ratio of fat to (carbohydrate + protein) ranging from 2:1 to 5:1. The proportion of total energy derived from fat ranges from 82-92 percent. Consuming a ketogenic diet produces a state of ketosis, which helps control seizures through an unknown mechanism. Fluid intake is restricted to maintain urine specific gravity at 1.020-1.025, since fluid intake dilutes blood ketones.

In different studies, 40-70 percent of patients following the diet experienced at least a 50-percent reduction in seizure frequency, and 10-33 percent became seizure-free. In many cases, medications could be discontinued or the dosages decreased. Two children with acquired epileptic aphasia were also successfully treated with this diet.<sup>32</sup> According to some research, myoclonic epilepsy responds best to the ketogenic diet.<sup>26</sup> However, another study found that the response to the diet did not vary significantly according to seizure type.<sup>25</sup> The diet is most effective in children ages 2-5 years, although patients of other ages have also benefited.<sup>26</sup>

To be effective, the diet must be followed strictly; if the patient discontinues it, seizures are likely to return within hours. Typically, treatment is initiated in the hospital, starting with a 36-hour water fast to induce ketosis; however, some investigators have found that it is not necessary to begin the diet with a fast.

The ketogenic diet is usually followed for about two years, after which the proportion of fat is reduced gradually over 6-9 months to that of a regular diet. After a patient has been on the diet for two years, seizures are less likely to recur on resumption of a normal diet. In some cases, the diet regimen is repeated if seizures recur.

There are some drawbacks to the ketogenic diet. Supplementation with multivitamins, calcium, and iron is necessary to prevent nutritional deficiencies. In addition, the ketogenic diet is unpalatable and is difficult for parents to administer.

### Ketogenic Diet for Adults

While most ketogenic diet studies have been conducted in children, one trial investigated its effect in 11 adults (ages 19-45 years; median, 32.2 years) with refractory epilepsy. At eight months of follow-up, three patients had a 90-percent reduction in seizure frequency compared with baseline, three patients had a 50- to 89-percent decrease, and one patient had a less-than-50-percent decrease. All types of seizures responded to the diet. Common adverse effects included constipation, menstrual irregularities, and increases in triglyceride levels and cholesterol/HDL ratios.<sup>33</sup>

### Ketogenic Diet with Medium-chain Triglycerides

The triglycerides of octanoic and decanoic acids (medium-chain triglycerides; MCTs) are more ketogenic than long-chain triglycerides present in dietary fats. Diets containing large proportions of MCTs (usually provided by supplementing with MCT oil) are also easier to prepare, more palatable, better tolerated, and require less carbohydrate and protein restriction than standard ketogenic diets.

The MCT ketogenic diet, which provides 50-70 percent of total energy in the form of MCTs, has been used as an alternative to the classic ketogenic diet.<sup>34-36</sup> In one study, adherence to this diet resulted in improvement or complete control of seizures in 44 percent of 50 children with drug-resistant epilepsy.<sup>37</sup> Children who have had a positive response to this diet may be able to taper off the diet after 3-4 years without experiencing a recurrence of seizures. While the MCT diet is frequently well tolerated, some patients abandon it because of gastrointestinal intolerance.

### Ketogenic Diet: Adverse Effects

The ketogenic diet has caused a number of adverse effects, some serious. Initiation of the diet can result in vomiting, hypoglycemia, or dehydration. In one study, serious adverse events (severe hypoproteinemia, Fanconi's renal tubular acidosis, or marked abnormalities on liver function tests) occurred in five of 52 children on a ketogenic diet.<sup>38</sup> Other potential side effects include increased bruising or other minor bleeding (in association with a prolonged bleeding time), constipation, and diarrhea.<sup>39,40</sup>

Long-term problems include moderate growth retardation, renal stones (5-8% of cases), gallstones, acidosis or metabolic problems (particularly during illness), recurrent infections, hypercholesterolemia, hyperuricemia, vitamin deficiency, and feeding problems. Prolonged ketosis may raise the serum level of phenobarbitone, which can result in alopecia, renal stones, and growth retardation.<sup>36</sup>

The ketogenic diet and anticonvulsant drugs both have an adverse effect on bone density, which can be partially reversed with vitamin D supplementation. Carnitine deficiency may also occur with the ketogenic diet, particularly in patients taking valproic acid. L-carnitine supplementation is recommended for patients who have low serum carnitine levels.<sup>41</sup>

Patients on the ketogenic diet must be monitored closely by a practitioner experienced in its use.

### Atkins Diet

The Atkins diet is a low-carbohydrate, high-fat diet used by millions of people for weight reduction. Like the ketogenic diet, the Atkins diet can induce a state of ketosis, but it has fewer restrictions on calories and protein. In addition, the Atkins diet does not require fluid restriction and does not need to be started in the hospital.

According to one study, the Atkins diet may be an effective alternative to the ketogenic diet in some children with intractable epilepsy. Twenty children (ages 3-18 years) with intractable epilepsy, with at least three seizures per week, who had been treated with at least two anticonvulsants, followed a modified Atkins diet (nature of the modification not specified) over a six-month period. Carbohydrates were limited to 10 g/day for the first month and consumption of fats was



## Review Article

encouraged. All children received vitamin and calcium supplements. At six months, 13 patients (65%) had more than 50-percent improvement and seven patients (35%) had more than 90-percent improvement (four were seizure-free). Small increases were seen in serum cholesterol and blood urea nitrogen levels during the study.<sup>42</sup>

In another study, two adults (ages 42 and 52) with epilepsy showed no improvement on the Atkins diet.<sup>43</sup> Table 1 weighs the evidence for various dietary/metabolic interventions.

increased xanthurenic acid excretion following a tryptophan load).<sup>51</sup> However, other factors may be involved as well, since there does not appear to be a strong relationship between low vitamin B6 levels and use of any specific anticonvulsant medication.

Vitamin B6 supplementation is clearly beneficial in cases of vitamin B6-dependent seizures. Some studies have demonstrated improvements in patients with non-vitamin B6-dependent epilepsy as well, although the research has produced conflicting results.

**Table 1. Dietary or Metabolic Factors Associated with Epilepsy**

Dietary or Metabolic Factors	Evidence
Reactive hypoglycemia/hyperinsulinemia	Clinical observations and lab findings
Food allergy	Case reports and uncontrolled clinical trial
Reaction to aspartame	Case reports
Reaction to monosodium glutamate	Case reports
Ketogenic diet	Multiple uncontrolled clinical trials
Atkins (very low carbohydrate) diet	Uncontrolled clinical trial

## Nutritional Supplements

### Vitamin B6

Experimentally-induced vitamin B6 deficiency resulted in seizures in rats<sup>44</sup> and swine.<sup>45</sup> In the early 1950s, numerous infants in the United States developed convulsions traced to the use of a formula that was deficient in pyridoxine.<sup>46,47</sup> Seizures also occurred in an infant fed exclusively on powdered goat's milk, which had undetectable levels of the vitamin. The seizures resolved after supplementation with vitamin B6.<sup>48</sup>

Vitamin B6 deficiency has been found in a high proportion of patients with epilepsy. Of 62 drug-treated epileptic patients, 55 percent had a subnormal blood level of pyridoxal phosphate (PLP).<sup>49</sup> In a study of 68 institutionalized patients with severe epilepsy, 37 percent had a reduced serum concentration of pyridoxal.<sup>50</sup> Low levels of vitamin B6 may be due in part to treatment with phenytoin, which has been associated with laboratory evidence of reduced vitamin B6 status (i.e.,

### Vitamin B6-dependent Seizures

Vitamin B6-dependent epilepsy is a rare inherited disorder that usually presents with intractable seizures in the first six months of life. The seizures can be completely controlled by administration of large doses of vitamin B6,<sup>52,53</sup> but if the condition is not treated promptly irreversible neurological damage may occur.

The diagnosis of vitamin B6 dependency can be established by intravenous administration of pyridoxine, which results in cessation of seizures within minutes. Intravenous administration of vitamin B6 to infants after a long period of convulsions has been followed in some cases by acute hypotonia; in one case assisted ventilation was required.<sup>54</sup> For that reason, resuscitation equipment should be available during a trial of intravenous vitamin B6.

Most patients can subsequently be maintained on 25-50 mg/day oral pyridoxine, although one child required 200 mg/day.<sup>55</sup> Long-term supplementation is necessary; discontinuation of pyridoxine after several



years of good seizure control has resulted in death from status epilepticus.

Some patients with vitamin B6-dependent seizures present with an atypical picture, including later onset (up to 19 months of age),<sup>56,57</sup> a seizure-free period before administration of pyridoxine, a long remission after withdrawal of pyridoxine, and an atypical seizure type. Because the spectrum of vitamin B6-dependent seizures is broader than initially thought, it has been recommended that a trial of vitamin B6 be considered in all infants and young children with intractable epilepsy.<sup>58</sup>

It is also recommended that women who have a child with vitamin B6 dependency receive vitamin B6 supplements during subsequent pregnancies.

### Vitamin B6 for Non-vitamin B6-dependent Epilepsy

Vitamin B6 supplementation has been reported to be beneficial in some, but not all, studies of patients with non-vitamin B6-dependent epilepsy.

Twenty-six children with epilepsy received 160 mg/day pyridoxine. Of the 19 patients with laboratory evidence of vitamin B6 deficiency (i.e., increased urinary excretion of xanthurenic acid following a tryptophan load), nine had complete or partial amelioration of seizures, and some of these patients were able to discontinue anticonvulsant medication. Of the seven patients with a normal tryptophan load test, none responded to pyridoxine.<sup>59</sup>

Of three children (ages 3-8 years) with epilepsy associated with impaired intellectual development, progressive emotional disturbances, and abnormal EEGs, all excreted elevated amounts of xanthurenic acid after a tryptophan load. After administration of 60-160 mg pyridoxine daily, tryptophan metabolism became normal and substantial clinical improvement occurred.<sup>60</sup>

Pyridoxine (20 mg, 3-6 times daily) was given for an unspecified length of time to 14 epileptic patients, ages 2-17 years. All patients had petit mal and one also had grand mal epilepsy. Seizures ceased in five patients and became less frequent in three others.<sup>61</sup>

Fifty-six epileptic children received 160-200 mg pyridoxine daily for at least six weeks. Significant clinical improvement was seen in five cases.<sup>62</sup>

A 23-year-old man with recurrent seizures presented with status epilepticus, which resolved immediately following intravenous administration of 60 mg PLP. Prior to treatment, his serum pyridoxine concentration was markedly decreased (80% below the lower limit of normal).<sup>63</sup>

Pyridoxine was given intravenously to infants and children with acute, recurrent seizures due primarily to acute infections. A dose of 30 or 50 mg/kg/day was administered in 100-250 mL of 10-percent glucose over 2-4 hours and given for a few days. Anti-epileptic drugs were used as appropriate. The treatment was rated "very effective" (i.e., duration and frequency of seizures decreased by more than 75 percent after 24 hours) in 62.5 percent of patients receiving pyridoxine compared with 26 percent of control patients ( $p < 0.001$ ); both doses of pyridoxine were equally effective. Aside from transient flushing, no adverse effects were seen.<sup>64</sup>

In other studies, pyridoxine in doses of 20-100 mg/day orally<sup>65,66</sup> or 300 mg/day parenterally<sup>67</sup> produced no clinical improvement in patients with various types of epilepsy.

### Pyridoxine versus Pyridoxal Phosphate

While most patients with vitamin B6-dependent seizures can be effectively treated with pyridoxine, some patients have only responded to PLP, the biologically active form of vitamin B6.<sup>68,69</sup> The average effective oral dose in six patients with PLP-responsive seizures was 30 mg/kg/day (range, 7-38 mg/kg/day), which was significantly higher than the average effective pyridoxine dose (18 mg/kg/day) in pyridoxine responders.<sup>70</sup> Because of superior efficacy in certain cases, PLP should be considered for first-line treatment of patients in whom a clinical trial of vitamin B6 is indicated. PLP should also be considered for patients with suspected vitamin B6-responsive seizures that are unresponsive to pyridoxine.

### Vitamin B6 in Clinical Practice

Vitamin B6 should be tried in all infants and young children with intractable epilepsy. For children and adults whose seizures are well controlled on medication, moderate doses of vitamin B6 (such as 10-50 mg/day) may be considered to prevent possible drug-induced vitamin B6 deficiency. Although larger doses





## Review Article

might be appropriate in selected cases, high-dose vitamin B6 appears to interfere with some anticonvulsant medications. In one study, supplementation with 80-200 mg/day pyridoxine reduced serum phenytoin and phenobarbitone levels in epileptic children.<sup>71</sup> In addition, long-term administration of 500 mg/day or more of pyridoxine has resulted in neurotoxicity in some adults,<sup>72</sup> which could presumably occur at lower doses in children.

One practitioner found that supplementation with 600 mg/day vitamin B6 reversed phenytoin-induced gingival hyperplasia in several patients; however, such high doses are probably excessive for most patients with epilepsy.<sup>73</sup> Lower doses might be effective for phenytoin-induced gingival hyperplasia, particularly when used in combination with a folic acid mouth rinse (see below).

Patients being treated with vitamin B6 should probably also receive a magnesium supplement, in view of evidence that these nutrients work together and anecdotal reports that vitamin B6 supplementation increases the requirement for magnesium.

### Magnesium

Severe magnesium depletion can cause seizures<sup>74,75</sup> or increase susceptibility to seizure-inducing stimuli.<sup>76</sup> Intravenously infused magnesium exerted an anticonvulsant effect against experimentally-induced epileptic foci in cats and dogs.<sup>77</sup> In humans, parenterally administered magnesium is an effective treatment for the seizures of neonatal tetany<sup>78</sup> and eclampsia and possibly for those associated with ethanol withdrawal and acute intermittent porphyria.<sup>79</sup>

Magnesium concentrations in serum and cerebrospinal fluid (CSF) were significantly lower in 40 patients with grand mal epilepsy than in controls.<sup>80,81</sup> Serum and CSF magnesium levels fell with increasing duration and frequency of seizures. Oral administration of magnesium has been associated in some cases with an improvement in EEG findings and a reduction in seizure frequency.<sup>82</sup>



### Vitamin E

Erythrocyte or plasma vitamin E concentrations were lower in children with epilepsy than in healthy controls. Vitamin E levels were lower in children receiving multi-drug therapy than in children receiving

single-drug therapy.<sup>83,84</sup> In some studies, vitamin E supplementation reduced seizure frequency, although no improvement was seen in other studies.

Twenty-four children (ages 6-17 years) with treatment-resistant epilepsy were randomly assigned to receive, in double-blind fashion, 400 IU/day d-alpha-tocopheryl acetate or placebo for three months. Of the 12 patients given vitamin E, 10 had a greater-than-60-percent reduction in seizure frequency (of that 10, six had a 90-100% reduction). None of the patients in the placebo group had a greater-than-60-percent reduction in seizure frequency ( $p < 0.05$  for the difference in response rate between groups). Vitamin E treatment had no effect on plasma levels of anticonvulsant medications.<sup>85</sup>

Thirty-five epileptic children and adults were randomly assigned to receive, in double-blind fashion, 250 IU/day vitamin E or placebo for three months. Anticonvulsants were continued as previously. Of the 12 adults receiving vitamin E, eight had a decrease in seizure frequency, two had an increase, and two were unchanged. Of the six children receiving vitamin E, two had a reduction in seizure frequency and four had no change. No changes were seen in the children and adults receiving placebo.<sup>86</sup>

In a double-blind study published as an abstract, supplementation with vitamin E reduced mean seizure frequency by 32 percent ( $p = 0.03$ ) in a group of severely mentally handicapped patients with treatment-resistance epilepsy. However, information was omitted regarding the dosage regimen and the response in the placebo group.<sup>87</sup>

In a study of 10 severely handicapped epileptic patients (ages 4-23 years) receiving anticonvulsants, supplementation with 100 IU/day dl-alpha-tocopheryl acetate for one month had no effect on seizure frequency.<sup>88</sup>

Forty-three teenagers and adults with uncontrolled epilepsy were randomly assigned to receive, in double-blind fashion, 600 IU/day vitamin E or placebo for three months. After a one-week washout period, each patient received the alternate treatment for an additional three months. Anticonvulsant medications were continued as previously. The mean seizure frequency decreased by 25.7 percent during the placebo period and by 13.8 percent during the vitamin E period compared with baseline.<sup>89</sup>

Although the research on efficacy is conflicting, vitamin E is relatively safe and may be considered for adjunctive treatment in epileptic patients, particularly children.

### Manganese

In rats, manganese deficiency increased susceptibility to electroshock-induced convulsions. In addition, hydralazine-induced seizures in rats were prevented by prior administration of manganese.<sup>90</sup>

In humans with epilepsy, whole-blood manganese levels were significantly lower by 20-41 percent than in controls.<sup>91-96</sup> Manganese concentrations in epileptic patients did not correlate with seizure frequency or the type, dose, or plasma levels of anticonvulsant medication. Concentrations of other minerals, such as zinc and copper, were generally normal, suggesting that the association between manganese deficiency and epilepsy was not due to general malnutrition. Patients whose epilepsy was a result of trauma had significantly higher blood manganese concentrations than patients with no history of trauma,<sup>92</sup> which suggests that manganese deficiency is a primary contributing factor, rather than a consequence, of epilepsy or its treatment.

One group of practitioners stated that unspecified doses of manganese were helpful in controlling epileptic seizures.<sup>97</sup> In a case report, a 12-year-old boy with poorly controlled epilepsy and a low blood manganese level experienced fewer seizures after treatment with 20 mg manganese daily. A dose of 10 mg/day was tried initially for three weeks, but was not effective.<sup>91</sup>

### Taurine

Taurine acts as a modulator of membrane excitability in the central nervous system by inhibiting the release of other neurotransmitters and decreasing mitochondrial release of calcium.<sup>98</sup> Taurine concentrations have been found to be elevated in serum, but decreased in the brain, of some patients with epilepsy. In contrast, serum concentrations of most other amino acids were lower in patients with epilepsy than in healthy controls. Taurine administration partially corrected these low serum amino acid concentrations.<sup>99-102</sup>

Taurine has been administered orally or intravenously at a wide range of doses (200 mg/day to 21 g/day) for varying periods of time to patients with severe,

intractable epilepsy. In some studies, a significant reduction in seizure frequency was observed,<sup>103-107</sup> whereas no benefit was seen in others.<sup>108</sup> According to one report, taurine was effective against partial epilepsy but had little effect on generalized epilepsy. The beneficial effects of taurine frequently diminished or disappeared after a few weeks of treatment. One possible explanation for the loss of efficacy is that high-dose taurine caused amino acid imbalances, as suggested by the appearance of generalized aminoaciduria in a patient during treatment daily with 2.0-2.5 g taurine. It has been suggested that the optimal dose of taurine to treat epilepsy might be in the range of 100-500 mg/day, and in one report a loss of antiseizure activity was seen in some patients when the dose was increased above 1.5 g/day. While additional studies are needed to determine taurine's optimal dosage range, no specific dosage regimen has been shown to produce long-lasting improvement of epilepsy.

### Dimethylglycine

Dimethylglycine, a metabolite of betaine, demonstrated anticonvulsant activity in mice in one study,<sup>109</sup> but not in another.<sup>110</sup>

In a case report, a 22-year-old mentally handicapped man with mixed complex, partial, and grand mal seizures had been having 16-18 generalized seizures per week, despite therapeutic levels of phenobarbital and carbamazepine. His mother began giving him 90 mg dimethylglycine twice daily because of a suggestion it might improve his stamina. Within one week his seizure frequency dropped to three per week. Two attempts to withdraw dimethylglycine resulted in a dramatic increase in seizures.<sup>111</sup>

In follow-up studies, administration of dimethylglycine to 24 epileptic patients in doses of 300-810 mg/day for up to 30 days did not produce any improvement.<sup>112,113</sup> It was suggested that the one patient who benefited from dimethylglycine may have had an isolated metabolic defect that was overcome by treatment with this compound.

### Thiamine

Severe thiamine deficiency can cause seizures in both alcoholic and non-alcoholic patients; these seizures are reversible with thiamine supplementation. Low





## Review Article

thiamine status was found in 25 percent of 620 epileptic patients attending an outpatient clinic in one study, and in 31 percent of 72 patients in another study.<sup>114,115</sup> In a placebo-controlled trial, supplementation of epileptic patients with 50 mg thiamine daily for six months was associated with significant improvements in tests of both verbal and non-verbal IQ.<sup>113</sup> Thus, suboptimal thiamine status may be a factor in the impaired cognitive function seen in some patients with epilepsy.

### **Folic Acid**

Seizures occur in some infants with cerebral folate deficiency, a syndrome that also includes slow head growth, psychomotor retardation, cerebellar ataxia, and other neurological abnormalities. This syndrome is caused by impaired transport of folate across the blood-brain barrier into the central nervous system. The transport defect can be overcome by administration of folinic acid (an active form of folic acid), which bypasses the blocked folate transport mechanism. There are several case reports in which administration of folinic acid (2.5-20 mg twice daily in one study, 0.5-1.0 mg/kg body weight per day in another) resulted in improvement or complete control of seizures in infants.<sup>116,117</sup>

In patients with seizures not due to cerebral folate deficiency, folic acid supplementation is of little or no benefit with respect to seizure control, and may even exacerbate seizures in some instances (see below). However, folate deficiency is common in patients with epilepsy and may have negative effects on other aspects of health. Subnormal serum or erythrocyte folate concentrations have been observed in 19-88 percent of patients with epilepsy in different studies.<sup>49,50,118-122</sup> Low folate levels were found more frequently among inpatients than outpatients, and in those with coexisting psychiatric illness than those without psychiatric illness. Folate deficiency is due primarily to the use of anticonvulsant medications (e.g., phenytoin, valproate, carbamazepine, phenobarbital, and primidone), which interfere with folic acid absorption.<sup>123-125</sup>

While correction of folate deficiency is desirable, administration of large doses of folic acid can decrease blood levels of phenytoin, phenobarbital, and carbamazepine,<sup>126-129</sup> potentially interfering with seizure control. An increase in seizure frequency has been seen in some,<sup>130</sup> but not all,<sup>131-133</sup> studies in which high-

dose folic acid (5 mg three times per day) was given to drug-treated epileptic patients. In addition to interfering with anticonvulsant medication, high-dose folic acid itself may be epileptogenic. Intravenous administration of 14.4 mg folic acid induced a tonic-clonic seizure in one epileptic patient, although other patients experienced no adverse effects from 75 mg folic acid given intravenously.<sup>134</sup> One woman with epilepsy had an increase in seizure frequency and severity after receiving 0.8 mg folic acid per day, which was prescribed because she was planning to become pregnant.<sup>135</sup> A cause-effect relationship in this case is uncertain.

Based on these observations, modest doses of folic acid should be used to treat folate deficiency in epileptic patients. A study of pregnant epileptic women taking anticonvulsant drugs found that a folic acid dose of 100-1,000 mcg/day was sufficient to prevent folate deficiency and did not impair seizure control.<sup>136</sup>

Folic acid has also been used to treat phenytoin-induced gingival hyperplasia. In a small double-blind study, use of a 0.1-percent folic acid mouth rinse for six months significantly reduced the severity of this condition, whereas a placebo was ineffective. Patients used 5 mL of the mouth rinse twice daily, spitting it out after rinsing for two minutes (this solution should not be swallowed, as doing so would provide 10 mg/day of folic acid). Oral, rather than topical, administration of folic acid (3-4 mg/day) produced little or no improvement in phenytoin-induced gingival hyperplasia.<sup>137,138</sup>

### **Biotin**

Serum biotin levels were below normal in 74 percent of 264 epileptic patients on long-term anticonvulsant therapy.<sup>139</sup> Low biotin levels appear to result from an acceleration of biotin catabolism by phenytoin, carbamazepine, and phenobarbital.<sup>140,141</sup> In addition, carbamazepine and primidone may inhibit intestinal absorption of biotin.<sup>142</sup> Interestingly, dermatitis and ataxia, side effects of many anticonvulsants, are also observed in patients with an inborn error of biotin-dependent enzymes.

There is no evidence that biotin supplementation interferes with the effect of anticonvulsants. To the contrary, correction of biotin deficiency might reduce seizure frequency, as suggested by the fact that biotin-responsive seizures have occurred in some patients with inborn errors of biotin metabolism.<sup>143</sup>



## Epilepsy

### Vitamin D

Patients taking anticonvulsants are at increased risk of developing vitamin D deficiency, apparently because these drugs induce liver enzymes that inactivate vitamin D.<sup>144,145</sup> Rickets,<sup>146</sup> osteomalacia,<sup>147</sup> and low bone mineral content<sup>148</sup> have been reported in drug-treated epileptic patients. The frequency with which these disorders occurred has varied widely in different studies, in part because of differences in sun exposure.

In patients with osteomalacia resulting from the use of phenytoin and phenobarbital, the amount of vitamin D3 needed to achieve positive calcium balance was approximately 975 IU/day.<sup>149</sup> In patients with low 25-hydroxyvitamin D levels who were taking phenytoin, carbamazepine, and phenobarbitone, either alone or in combination, the amount of vitamin D3 required to maintain a normal serum 25-hydroxyvitamin D concentration (15 ng/mL or greater) ranged from 400 to 4,000 IU/day, with 72 percent of patients requiring 2,400 IU/day or more.<sup>150</sup>

### Essential Fatty Acids

Five severely mentally handicapped patients (ages 12-26 years) with more than 3-4 grand mal seizures per month received a daily supplement providing 900 mg eicosapentaenoic acid (EPA), 2.3 g docosahexaenoic acid (DHA), and 50 mg alpha-linolenic acid. All five patients experienced a marked reduction in both frequency and severity of grand mal seizures.<sup>151</sup> In a double-blind study that included 57 adults (mean age, 39 years), supplementation with fish oil (providing 1 g/day EPA and 0.7 g/day DHA) reduced seizure frequency during the first six weeks of treatment, but the beneficial effect was not sustained thereafter.<sup>152</sup>

In contrast to the possible beneficial effect of omega-3 fatty acids, the omega-6 fatty acids in evening primrose oil may have deleterious effects in some patients with epilepsy. There are several case reports in which administration of evening primrose oil appeared to exacerbate or unmask temporal lobe epilepsy.<sup>153-155</sup>

### Carnitine

Treatment of children with valproic acid, particularly in combination with other anticonvulsant drugs, reduced total and free carnitine concentrations and increased plasma ammonia concentrations (a

manifestation of carnitine deficiency). Carnitine levels in patients taking anticonvulsants other than valproic acid were normal.<sup>156,157</sup> A consensus statement by a panel of pediatric neurologists concluded that L-carnitine supplementation is indicated for patients with symptomatic valproic acid-associated hyperammonemia, multiple risk factors for valproic acid hepatotoxicity, or renal-associated syndromes; infants and young children taking valproic acid; patients with epilepsy using the ketogenic diet who have low serum carnitine levels; patients receiving dialysis; and premature infants receiving total parenteral nutrition. The panel recommended an oral L-carnitine dosage of 100 mg/kg/day, to a maximum of 2 g/day. Intravenous L-carnitine was recommended for valproic acid-induced hepatotoxicity, overdose, and other acute metabolic crises associated with carnitine deficiency.<sup>41</sup>

### Vitamin K

A hemorrhagic diathesis associated with low prothrombin levels occurs in about 27 percent of infants of mothers receiving anticonvulsant medication. Fourteen pregnant epileptic women received 20 mg/day vitamin K1 for two weeks before delivery. No hemorrhages occurred in the babies and prothrombin times were all normal at birth. The authors of this study suggested that vitamin K1 should be given routinely to drug-treated epileptic women near the end of pregnancy.<sup>158</sup>

### Hormones

#### Melatonin

In one study, 3 mg melatonin was given each night for three months to six children (ages 2-15 years) with severe, intractable seizures. The mean seizure frequency decreased from 3.6 per day at baseline to 1.5 per day during treatment (58% reduction;  $p < 0.05$ ).<sup>159</sup> Melatonin has also been used in doses of 2-10 mg before bedtime to treat sleep disturbances in children with epilepsy. Melatonin treatment was associated with an increase in seizure frequency in some patients and a decrease in others.<sup>160-162</sup>

Because melatonin appears to have unpredictable effects on seizure frequency, it should be used with caution in patients with epilepsy.



## Review Article

### Progesterone

According to one study, progesterone may be beneficial for women who have seizure exacerbations at specific times during the menstrual cycle. Twenty-five women with cyclic exacerbation of complex partial or secondary generalized motor seizures of temporal origin received progesterone lozenges (200 mg 3 times per day). Women with perimenstrual exacerbations received treatment on days 23 to 25 of each cycle; women who had exacerbations during the entire luteal phase were treated from days 15 to 25 of each menstrual cycle. In both groups of women, progesterone was tapered after day 25 and discontinued by day 28. Progesterone was well tolerated by 23 of the 25 women. Two women experienced asthenia and emotional depression, which resolved within one day of discontinuing treatment. Eighteen women (72%) experienced a decline in seizure frequency during the three-month treatment period, compared with the three months prior to therapy ( $p < 0.01$ ). Among the 23 women who continued treatment, the average frequency of complex partial seizures declined by 54 percent ( $p < 0.01$ ) and the frequency of secondary generalized motor seizures declined by 58 percent ( $p < 0.02$ ).<sup>163</sup>

### Conclusion

A number of different dietary modifications, nutritional supplements, and hormones may help prevent seizures or improve other aspects of health in patients with epilepsy. Table 2 summarizes the strength of the evidence for potential nutrient and hormone interventions. Supplementation with specific nutrients should also be considered for the prevention and treatment of nutritional deficiencies resulting from anticonvulsant drugs. In most cases, nutritional therapy is not a substitute for anticonvulsant medications. However, in selected cases, depending on the effectiveness of the interventions, dosage reductions or discontinuation of medications may be possible.

Because much of the research on epilepsy management with diet, nutrients, and hormones is preliminary, there are few clear guidelines on when and how to use the various interventions described in this article. However, consideration of basic aspects of nutrition and metabolism should aid the clinician in evaluating this research and making rational clinical decisions.

**Table 2. Nutrient and Hormone Interventions in Epilepsy**

Nutrient	Evidence
Vitamin B6	Case reports, uncontrolled clinical trials
Magnesium	Clinical observations and lab findings
Vitamin E	Double-blind trials
Manganese	Clinical observations and lab findings
Taurine	Uncontrolled trials
Dimethylglycine	Case report, negative follow-up studies
Thiamine (to improve cognitive function)	Clinical observations and lab findings
Folic acid	Clinical observations and lab findings
Biotin	Clinical observations and lab findings
Vitamin D	Clinical observations and lab findings
Omega-3 fatty acids	Uncontrolled and double-blind trials
L-Carnitine (to prevent valproate toxicity)	Clinical observations and lab findings
Vitamin K (to prevent drug-induced deficiency)	Uncontrolled trial
Melatonin	Uncontrolled trial
Progesterone	Uncontrolled trial

For example, hypoglycemia should be considered a potential triggering factor in patients who develop seizures in the late morning or late afternoon or when a meal is missed. Food allergy might be a contributing factor in epileptic patients who have other manifestations of possible allergy, such as migraines, asthma, or a history of recurrent ear infections in childhood. A trial of manganese supplementation would seem appropriate for patients with low whole-blood manganese concentrations. An empirical trial with vitamin E would seem reasonable for many patients with epilepsy, particularly children. Supplementation with magnesium (200-600 mg per day) and modest doses of vitamin B6 (such as 10 mg per day) for general nutritional support would also be reasonable for many patients, in light of evidence that a large proportion of the population has suboptimal intakes of these nutrients.<sup>164,165</sup> Larger doses of vitamin B6 could be considered for patients whose epilepsy is not adequately controlled by other treatments.

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