Childhood Absence Epilepsy: Putative Complementary Diet and Orthomolecular Treatment Options; with an Addendum to an Earlier Report

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Abstract *This paper discusses childhood absence epilepsy (CAE), and reviews outcomes from standard anti-seizure medication. Given the possibility of pharmacoresistance and the fact that treatment-resistant epilepsy in adulthood can be life-threatening, other complementary approaches are discussed. Dietary approaches, such as the ketogenic diet, modified Atkins diet, and the Paleolithic ketogenic diet are reviewed. The modified Atkins diet appears to have the most robust evidence of efficacy compared to the other diets for CAE, and can be offered to patients, possibly as an alternative to anti-seizure medication. Specific orthomolecular approaches, i.e., gamma-aminobutyric acid and phosphatidylserine, are advocated as complementary treatments since compelling (preliminary) data shows significant reductions in seizure activity among subjects of all ages with absence seizures. Additional information pertaining to a prior published report is also included. This advances a transdiagnostic orthomolecular approach to complement anti-seizure medication with a restorative regimen among treatment-resistant patients with epilepsy.*

Introduction

The disease of epilepsy is marked by repeated, but intermittent episodes of seizure activity "in which synchronous activity of nerve cells increases so that a gigantic hyperpolarization of neurons spreads over a large area in an atypical and abnormal manner" (Banich & Compton, 2011, p.491). A form of generalized seizures, childhood absence epilepsy (CAE) or childhood absence seizures (formerly referred to as petit mal seizures), involves the entire body when seizure activity is present, and accounts for 10-17% of all childhood-onset epilepsy cases (Berg et al, 2000; Jallon, Loiseau, & Loiseau, 2001). According to The International League Against Epilepsy, CAE is characterized by rather frequent staring spell absences (happening several to possibly numerous times each day) in children of school age - usually having a peak manifestation at around six to seven years of age - and electroencephalographic (EEG) findings of bilateral, synchronous, and symmetric spike-wave discharges at 3 Hz (Proposal for revised classification of epilepsies and epileptic syndromes, 1989).

If one were to observe a child having absence seizures, there would be an "abrupt and brief impairment of consciousness, with interruptions of the ongoing activity, and usually unresponsiveness" lasting anywhere from several to 20 seconds, which is then

followed by a sudden "resumption of the pre-absence activity" as though it had never been interrupted (Panayiotopoulos, 1999, p. 351). While CAE typically presents with impairment of consciousness, many patients also exhibit other clinical manifestations, such as mild clonic jerks (e.g., of the eyelids or corner of the mouth), atonic components (e.g., relaxation of grip and dropping of the arms), tonic muscular contractions (e.g., arching of the trunk), automatisms (e.g., aimless walking or lip licking), and even autonomic components like pallor, sweating, and less commonly, urinary incontinence (Panayiotopoulos, 1999).

This form of epilepsy is often thought to be rather benign, but yet the remission rates are variable, and affected children can experience cognitive deficits and long-term psychosocial difficulties (Bouma, Westendorp, Dijk, Peters, & Brouwer, 1996; Wirrell et al, 1997; Pavone et al, 2001). A study identified some of the general psychosocial problems encountered by children with CAE, such as social isolation and low self-esteem, but these children also experienced higher rates of comorbid psychiatric symptoms, such as anxiety (nervousness and thought rumination), and depression (sadness and crying) (Vega et al, 2011).

With respect to mortality, a population-based cohort study that followed patients for 40 years demonstrated that being diagnosed with epilepsy during childhood was associated with a substantial risk of epilepsy-related death that persisted into adulthood (Sillanpää & Shinnar, 2010). Specifically, "the risk of sudden, unexplained death among subjects with epilepsy was 7% (95% CI, 5 to 12) among all subjects and 12% (95% CI, 8 to 20) among those who were not in 5-year terminal remission and not receiving medication" (p.2527). The risk of death can also be ascertained by looking at the hazard ratio (HR), which (based on this study) refers to the probability of dying from epilepsy compared to deaths among individuals without epilepsy. For instance, among subjects that have not achieved a 5-year terminal remission, the HR for sudden, unexplained deaths was determined to be 5.2 (95% CI, 1.4 to 18.5). For epilepsy-related deaths among subjects that have not achieved a 5-year terminal remission, the HR was determined to be 6.4 (95% CI, 2.2 to 18.8). As can be seen, a diagnosis of epilepsy in childhood presents serious threats to an individual's overall mortality especially if the disease remains poorly controlled or resistant to treatment.

Given how challenging CAE can be, exploring complementary avenues of treatment could potentially enhance outcomes from standard treatment. The first part of this paper will review a highly-publicized study that assessed the efficacy of standard treatment among subjects with CAE. Then the paper will review several complementary approaches that have efficacy in reducing seizure activity among subjects with CAE. The final part on CAE will highlight a case in which an integrative approach demonstrated a cessation of seizure activity in a patient with CAE, although this is very preliminary. This paper will also present an addendum to a prior report (i.e., The Adjunctive Treatment of Epilepsy with Orthomolecular Substances) published in this journal (Prousky, 2014).

Outcomes from Standard Treatment

As was mentioned earlier, treatment outcomes for CAE are variable. The most widely regarded study on the treatment for CAE evaluated the most commonly prescribed anti-seizure medications for efficacy - i.e., ethosuximide (ES), valproic acid (VA), and lamotrigine (LT) - in a double-blind, randomized, controlled clinical trial (Glauser et al, 2010). Subjects (n=453; median age: 7 years and 5 months; age range: 2.5-13 years old) were randomized to one of these treatments over a 16-week period (sometimes, up to 20 weeks). All the subjects had CAE of new onset. Doses of all medications were increased every 1-2 weeks over the study period until the subjects became seizure-free, or adverse effects limited the prescribed dose.

The ES group (Glauser et al, 2010) was comprised of 156 patients, of which 2 dropped out. Subjects began with daily doses of 10 mg/kg of body weight, and were titrated up to doses as high as 60 mg/kg of

body weight (maximal daily dose of 2,000 mg was prescribed if necessary). The mean daily dose (±SD) for 94 subjects in the ES group at final evaluation was 33.5±15.3 mg/kg of body weight, with 17.5% of the group requiring the maximal dose of medication. The results showed the following:

a. Lack of seizure control in 14% ([22/154]*100);
b. Intolerable adverse effects in 24% ([37/154]*100);
c. Adverse psychological effects in 8% ([12/154]*100);
d. Attentional problems in 33% ([35/106]*100);
e. Overall treatment failure 47% ([73/154]*100); and
f. Seizure-free 53% ([81/154]*100).

Possible adverse effects from ES include: gastrointestinal symptoms, drowsiness, lethargy, mood changes, headache, visual changes, allergic rashes (about 5% of patients), aplastic anemia, and agranulocytosis (Wahab, 2010).

The VA group (Glauser et al, 2010) was comprised of 148 patients, of which 2 dropped out. Subjects began with daily doses of 10 mg/kg of body weight, and were titrated up to doses as high as 60 mg/kg of body weight (maximal daily dose of 3,000 mg was prescribed if necessary). The mean daily dose (±SD) for 104 subjects in the VA group at final evaluation was 34.9±15.8 mg/kg of body weight, with 20.5% of the group requiring the maximal dose of medication. The results showed the following:

a. Lack of seizure control in 12% ([18/146]*100);
b. Intolerable adverse effects in 24% ([35/146]*100);
c. Adverse psychological effects in 14% ([20/146]*100);
d. Attentional problems in 49% ([52/106]*100);
e. Overall treatment failure 42% ([61/146]*100); and
f. Seizure-free 58% ([85/146]*100).

Possible adverse effects of VA include: tremor, weight gain, dyspepsia, diarrhea, peripheral edema, pancreatitis, hair loss, thrombocytopenia, agranulocytosis, polycystic ovaries, Stevens-Johnson syndrome, hepatotoxicity, and teratogenicity (Wahab, 2010).

The LT group (Glauser et al, 2010) was comprised of 149 patients, of which 3 dropped out. Subjects began with daily doses of 0.3 mg/kg of body weight, and were titrated up to doses as high as 12 mg/kg of body weight (maximal daily dose of 600 mg was prescribed if necessary). The mean daily dose (±SD) for 96 subjects in the LT group at final evaluation was 9.7±6.3 mg/kg of body weight, with 58.9% of the group requiring the maximal dose of medication. The results showed the following:

a. Lack of seizure control in 47% ([69/146]*100);
b. Intolerable adverse effects in 17% ([25/146]*100);
c. Adverse psychological effects in 6% ([9/146]*100);
d. Attentional problems in 24% ([25/104]*100);
e. Overall treatment failure 71% ([103/146]*100); and
f. Seizure-free 29% ([43/146]*100).

Possible adverse effects of LT include: dizziness, sedation, headache, diplopia, ataxia, skin rash, and Stevens-Johnson syndrome (Wahab, 2010).

As can be ascertained from Glauser et al (2010), close to 50% of the subjects (i.e., 209 of the 446 children) became seizure-freeduring the study period. Overall treatment failure occurred in 42-71% of subjects (depending on the anti-seizure medication taken), which meant that a fairly large percentage of subjects failed to achieve complete remission of their seizures during the study. This is a much larger percentage when compared to the inefficacy of anti-seizure medications in general that fail to control seizures in about 30% of patients due to pharmacoresistance (Wahab, 2010). Even when treatment is initiated early (as in CAE), there is no guaran-

tee of long-term remission despite the fact that most patients with epilepsy are treated with anti-seizure medication for the duration of their lives (Wahab, 2010).

With respect to dosing, the average doses in the trial were higher than the initial doses, and maximal doses were needed in about 20% of patients from the ES and VA groups, and almost 60% of patients from the LT group (Glauser et al, 2010). Intolerable side effects were identified in about 20% of subjects, suggesting that the tolerability of the medications was sufficient for the majority of subjects. Problems with attention were evident among a significant minority of the study subjects, and persisted even when they became seizure-free, suggesting that such problems might be a core feature of CAE for some children. Overall, the results suggested that ES is the most indicated medication for initial empirical treatment, even though empirical treatment "fails in about 50% of newly diagnosed cases," and is not effective should the seizures evolve into the generalized tonic-clonic type (p. 7).

Complementary Dietary interventions: Ketogenic diet, Modified Atkins Diet, and the Paleolithic Ketogenic Diet

Only one published study has reviewed the clinical outcomes from either a ketogenic diet (KD) or modified Atkins diet (MAD) among patients with CAE (Groomes et al, 2011). For readers interested in understanding the macronutrient and other differences between a KD and MAD, please see Table 2 (p.439) from Kossoff, Cervenka, Henry, Haney, and Turner (2013).

The researchers (Groomes et al, 2011) performed two types of evaluations. The first involved a historical review that assessed publications from 1922 to 2009 related to both the KD and symptoms suggestive of absence seizures (e.g., petit mal), or when the diagnosis was confirmed by standard methods of the time. The second review involved patients at Johns Hopkins Hospital who were prescribed the KD or MAD for CAE, and followed from 1993 to 2009.

The historical review (n=133) demonstrated the following results from the KD:

a. A total of 69% ([92/133]*100) had a greater than 50% reduction in seizures from the diet;
b. A total of 34% ([45/133]*100) became seizure-free for some period of time on the diet;
c. It took between 3 days and 3 months to respond to the diet; and
d. The diet was continued for 9 weeks, and as long as 3 years among some patients.

The Johns Hopkins study (n=21) as reported by Groomes et al (2011) demonstrated favourable results from either the KD (n=8) or MAD (n=13). With respect to the KD, a total of 25% ([2/8]*100) became seizure-free. With respect to the patients on the MAD, the amount of seizures at baseline (i.e., before dietary changes were made) ranged from 1-150 seizures daily. During the evaluation period, 12 patients were on 1 anti-seizure medication; 7 were on 2 anti-seizure medications; 1 patient was on 3 anti-seizure medications; and 1 patient was on no medication. The patient on no medication, or those on only 1 anti-seizure medication fared much better compared to patients on 2 or more anti-seizure medications. The more medicated the patients were the less they benefited from the diet. The following results were obtained from the MAD study:

a. A total of 15% ([2/13]*100) became seizure free, with a total of 31% ([4/13]*100) demonstrating greater than 90% reduction in seizures (i.e., meaning that a total of 46% of patients on the diet had an excellent clinical response);
b. A total of 46% ([6/13]*100) of patients experienced greater than 50% reduction in seizures; and
c. A total of 8% ([1/13]*100) of patients showed no improvement from the diet.

Overall, it took between 1-3 months to respond to these diets, with greater improvements happening the longer the diet was maintained. Patients did better at 3 months compared to 1 month. A total of 48% ([10/21]*100) had a greater than 90% reduction in seizures, and 86% ([18/21]*100) had a greater than 50% reduction in seizures. The researchers concluded that either diet

appears to have efficacy for patients with intractable CAE because the majority of patients responded well, and many had periods where they had no seizure activity. As a result, the researchers emphasized that further prospective studies of diets for CAE are warranted.

Adverse effects and other aspects of the KD have been summarized by Kossoff, Zupec-Kania, and Rho (2009). The long-term adverse effects include carnitine deficiency, growth retardation, gastrointestinal symptoms, increased lipids, and kidney stones. More serious adverse effects, according to these researchers, have been reported in fewer patients and include cardiac abnormalities (due to selenium deficiency), Fanconi renal tubular acidosis, and pancreatitis. Moreover, children on a KD for more than 6 years are at greater risk of developing bone fractures, growth retardation, and kidney stones, but surprisingly not lipid abnormalities. There are ways of mitigating some of these risks by using a broad-spectrum micronutrient supplement, adding medium chain triglycerides and carnitine to control the dyslipidemia, and adding potassium citrate at the onset of the diet to increase the urine pH and lower the risk of developing kidney stones. Children that demonstrate a greater than 50% seizure response from the KD are encouraged to remain on the diet for at least 2 years. There is data demonstrating that among children who experienced seizure freedom from the KD, 80% remained seizure-free even 2 years after discontinuing the diet.

The MAD is associated with fewer adverse effects and better compliance. In a review paper by Sharma and Jain (2014), the more common adverse effects include constipation and vomiting at the onset of treatment, but these gastrointestinal effects typically improve the longer the diet is maintained. Some children can lose weight on the diet, but they tend to be heavier or overweight to begin with. Total cholesterol levels do increase, but the elevations are half that of the levels associated with a KD. Kidney stones, while a concern, have not been reported among children on the diet. It is probably a good idea for the child to take a broad spectrum micronutrient supplement to offset potential deficiencies and/or insufficiencies resulting from the diet. As mentioned earlier, it takes around 1-3 months to determine if the diet is efficacious. If the response is positive, the diet should be followed for at least 2 years before it is discontinued to determine if it is required on a long-term basis.

The only other dietary intervention for CAE that has been reported is that of a Paleolithic ketogenic diet. A case report (Clemens, Kelemen, Fogarasi, & Toth, 2013) documented the efficacy of the diet for a 7-year-old girl with CAE. The patient was having approximately 50 seizures daily prior to the dietary changes. Once the diagnosis was confirmed following an EEG study, the patient was offered VA, but the parents refused due to their concerns about the medication's adverse effects. The parents then consulted with a physician experienced with the clinical uses of the Paleolithic ketogenic diet, and decided to place their child on it. Essentially, the diet consisted of meat, offal (refers to internal organs and entrails of butchered animals), fish, egg, and animal fat without any caloric restrictions. To review what a sample Paleolithic ketogenic diet looks like, please see Table 1 (p. 74). The patient's diet was complemented with vitamin D3 (2,000 IU/day), and omega-3 essential fatty acids (500 mg/day). It took 6 weeks for the child to become seizure-free on this diet, and this result was maintained for 20 months (i.e., before the paper was published).

No adverse effects could be attributed to the diet. At three months, the patient's daily carbohydrate intake was gradually increased to include low glycemic index vegetables while the other restrictions of the diet remained. Laboratory measurements carried out at 6 weeks and then at 14 months did not show any clinically concerning abnormalities that could be attributed to the diet, except for the moderate, but clinically insignificant increase in the patient's total cholesterol. The patient's low-density lipoprotein cholesterol was moderately elevated at the 6 weeks mark, but was not remeasured at the 14 month mark, so it is not possible to know if this elevation persisted. At 14 months the pa-

tient also had a video EEG that evaluated her sleep, and no evidence of any epileptic activity was found. The patient gained 3 kilograms and grew 6 centimeters while on the diet, and the parents noted improvements in the patient's mood and social functioning. Classic ketogenic diets, on the other hand, can result in notable adverse effects, which were described earlier. Of interest, prior to the diet the patient was considered to be a special needs student, but after being on the diet she was able to perform well enough academically to attend regular school. The only issue that remained, and was not helped by the diet, was that of nocturnal enuresis.

Putative Mechanisms of Action

According to Kossoff et al (2009), the KD interfaces with "a multiplicity of novel molecular targets that respond to a fundamental shift from glycolysis to fatty acid oxidation," but the anti-seizure and possibly the neuroprotective effects of the diet remain unconfirmed (p. 982). Even so, this team of researchers discuss animal data linking the mechanism of the KD to: (1) specific ketone bodies (i.e., acetoacetate and acetone) which have anti-seizure effects; (2) decreasing the spontaneous firing rate of GABA (gamma-aminobutyric acid)-ergic neurons in the substantia nigra culminating in membrane hyperpolarization (i.e., lessens neuronal excitation in "other seizure-prone brain areas"); and (3) the abrogation of glycolytic flux (p. 983). Also, the diet does seem to offer some degree of neuroprotection since studies on children have shown that 20% can stop their anti-seizure medications without any recurrence of seizures; and among those that discontinued the diet before reaching 1 year, 46% had a greater than 50% reduction in seizures for 3-6 years after (p. 983). Taken together, it is likely that the KD (and any similar variation, such as the ketogenic Paleolithic diet) exerts neuroprotective and/or antiepileptogenic effects.

With respect to the MAD, it is unclear if ketosis is the mechanism behind the diet's efficacy since many children shift out of ketosis over time, yet still have adequate seizure control (Kossoff et al, 2006). It is possible that seizure control results from the initial ketosis induced by the diet, and/or that "low levels of stable ketosis" result in the long-term improvement (Kossoff et al, 2013, p. 440). At this point, it remains unclear how the MAD results in seizure control, but the likely answer involves some combination of increased fat utilization, the elevation of ketones, and other metabolic effects.

Discussion

In my opinion, the MAD is the most promising of all the diets, even though the Paleolithic ketogenic diet was effective in the published case. The MAD diet shows a similar efficacy to that of anti-seizure medication, but has fewer adverse effects. Kossoff et al (2013) recommends that the MAD could be offered to new-onset epilepsies for a trial period of 1-2 months, but if unsuccessful, the diet would then be discontinued and anti-seizure medications would be initiated.

Only one of the patients with CAE from the Johns Hopkins study (Groomes et al, 2011) was on no anti-seizure medication. This patient became seizure-free on the MAD. Thus, these results, except where noted, showed marked clinical benefits when the MAD was added to anti-seizure medication. In the case report, the child with CAE was on no anti-seizure medication and became seizure-free on the Paleolithic ketogenic diet (Clemens et al, 2013).

The fact that diet is not usually advocated as first-line treatment does not mean that it is less effective, and one could argue that it might very well be more effective than anti-seizure medication since it has a much more favourable safety (i.e. adverse effect) profile. The fact that 2 patients with CAE on no anti-seizure medication became seizure-free suggests more patients with CAE could benefit in a robust manner from diet alone without resorting to anti-seizure medication as first-line treatment. The only issue is that of compliance since the MAD (or Paleolithic ketogenic diet) are much less convenient than anti-seizure medication. Also, it would likely take around 1-3 months on the MAD, and 6 weeks on the Paleolithic ketogenic diet (assuming the results of the case report are generalizable) to see discernable clinical benefits,

whereas anti-seizure medications typically show benefits earlier even though they do not always put seizures into long-term remission.

Complementary Orthomolecular Treatments - GABA and Phosphatidylserine

GABA

While researching the therapeutic aspects of GABA (i.e., an orthomolecule), I located one of the earliest reports documenting the putative efficacy of GABA among patients with various types of seizures (Tower, 1960). The report contains rich and useful clinical information that was previously unknown to me. Orthomolecules refer to substances found naturally or normally in the human body, such as amino acids, essential fatty acids, hormones, minerals, and vitamins.

The first part of the report presents data on GABA and glutamine metabolism in incubated slices of normal and epileptogenic cerebral cortex (Tower, 1960). In epileptogenic brain slices from humans, the addition of GABA during in vitro incubation completely resolved the abnormality of glutamic acid metabolism (Table 1, p. 563). Based on these results, the conclusion was that "glutamic acid and GABA metabolism may be impaired in most seizure states" (p. 563). These results are consistent with a litany of publications that have implicated abnormal glutamic acid and GABA metabolism in the genesis and chronicity of seizures, including patients with absence seizures (see, for example, Engelborghs, D'Hooge, & De Deyn, 2000).

Another part of the report (Tower, 1960) documented the adverse reactions among 3 patients that were given GABA only once at a dose of 2 mM/kg (or 0.2 g/kg), and three non-epileptic (i.e., normal) adults that were given a dose of 1 mM/kg (or 0.1 g/kg) only once (p. 566). I have included all the adverse effects that were noted following the oral administration of GABA below:

"...within minutes after ingestion of 2 mM/kg of GABA they experience a sensation of warmth, which coincides with observed flushing of face and extremities. This reaction is often rapidly followed by a general malaise of uneasy feeling, which may be accompanied by nausea and rarely emesis. Two patients have experienced recurrent diarrhea. In addition, the majority of patients experienced paresthesia of the extremities more or less coincident with the foregoing signs and symptoms. Three normal adults on our clinical staff also experienced these reactions after ingestion of a dose of 1 mM/kg. The duration of these various side effects has generally been 10 and 90 min, and tolerance to the compound as far as flushing, malaise and paresthesias are concerned generally develops within a few weeks. In 3 cases the gastrointestinal symptoms have persisted for a number of months, but in no case have been severe enough to necessitate abandoning the therapeutic trial (pp. 566 & 568)."

Table 1 (below) lists the possible adverse effects from the oral administration of GABA, including transient throat irritation or self-limited breathing problems that several patients have reported to me; none have been life threatening requiring emergent medical management.

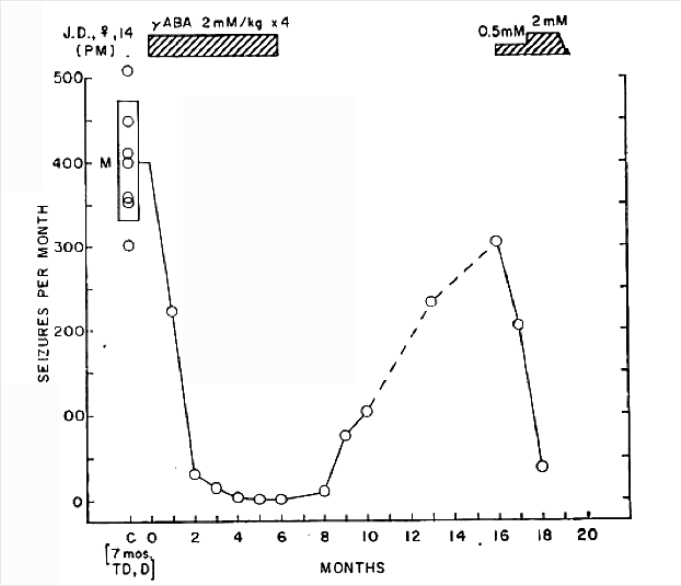
Table 1. Possible systemic adverse effects following the oral administration of a very high dose of GABA

1.	Flushing
2.	Paresthesias
3.	Malaise
4.	Nausea, vomiting
5.	Diarrhea
6.	Transient throat irritation or self-limited breathing problems

When explaining the mechanism responsible for these observed adverse effects, Tower (1960) believed they were "peripherally rather than centrally mediated and that they may well be autonomic, perhaps vasomotor phenomena" (p.568). Moreover, in commenting further about GABA's adverse effects, he reiterated that none were severe or serious, and mentioned that "some of our patients have been on daily doses of 8 mM/kg for a year or more with no indication of chronic or cumulative toxicity" (p.568).

Then the report discussed results from the chronic oral administration of GABA among several patients under the subheading, "Anticonvulsant Effects of GABA in Man" (Tower, 1960, p. 568). The complete report involved a total of 11 patients that were given a regular daily schedule of oral GABA and were followed for 3 months, and some for as long as 2 years. The first case involved a 14-year-old girl with petit mal-type seizures. For 7 months the patient had been treated with adequate doses of anti-seizure medications (i.e., trimethadione and diphenylhydantoin), but still experienced 300-500 seizures per month (mean: 402±68 seizures per month). When the patient was given oral GABA only (2 mM/kg 4 times daily or 0.8 g/kg daily), there was a "prompt and dramatic reduction of seizure frequency essentially to zero within 2 months" (p. 568). The patient remained essentially seizure-free for 6 months, and then when GABA was discontinued there was a prompt resumption of seizure activity (at least 5-10 daily; 200-300 seizures per month) during the approximate 8 months without it (**Figure 1,** below). GABA was resumed slowly (0.5 mM/kg 4 times daily), and then increased to 2 mM/kg 4 times daily, at which point "a very prompt and undoubted decrease in frequency took place" (p. 569).

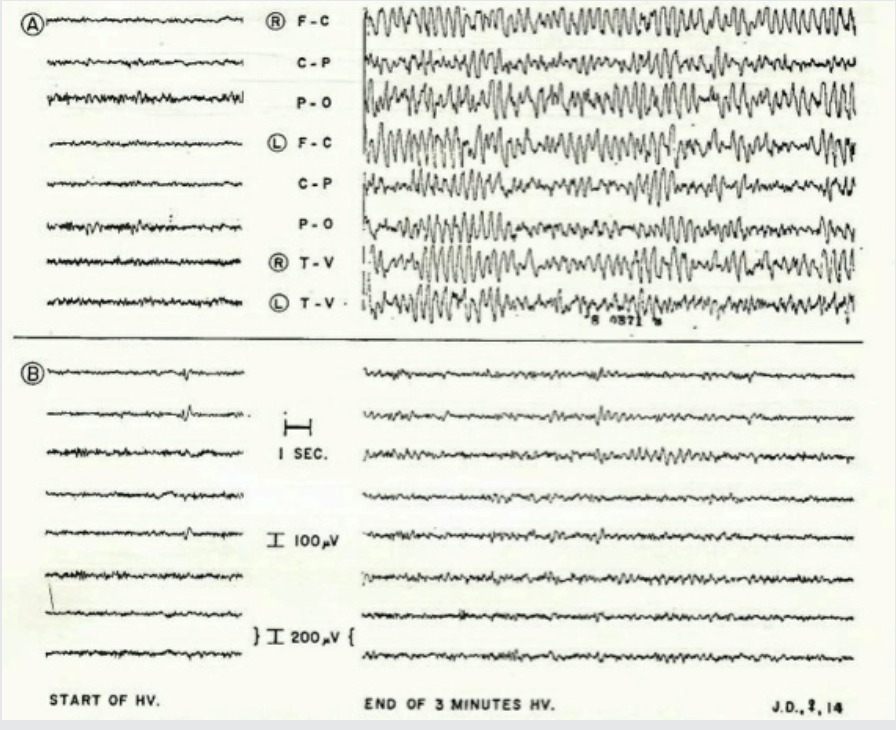
Figure 1. Monthly seizure record of J.D., 14-year-old female. Petit mal (PM) seizure frequency for the 7-month control period (C) while on trimethadione (TD) and diphenylhydantoin (D) had a mean value (M) of 402 (±68). Standard deviation of mean value indicated by length of the box (Tower, 1960, p. 569). Reprinted with permission from: Tower, D. B. (1960). The administration of gamma-aminobutyric acid to man: Systemic effects and anticonvulsant action. In Inhibition in the nervous system and gamma-aminobutyric acid (pp. 562-578). New York, NY: Pergamon Press, Inc.



The EEG prior to the readministration of GABA revealed "virtually continuous paroxysmal high voltage epileptiform activity induced after 2 min of hyperventilation and persisting to the end of the full 5 min test period" (p. 569). At the end of the 18 month mark (after having resumed GABA for 2 months) - with an EEG recording made under similar testing circumstances (i.e., to control for any confounds) - the results showed that "during hyperventilation no paroxysmal high voltage activity was observed, and only three brief (2-4 sec) bursts appeared during the whole 5 min hyperventilation test period" (p. 569). Thus, the paroxysmal high-voltage epileptiform activity in the patient's EEG completely disappeared after the readministration of oral GABA during the second trial, with the frequency of seizures having reduced to less than 40 per month (**Figure 2,** below).

Other patients were administered GABA

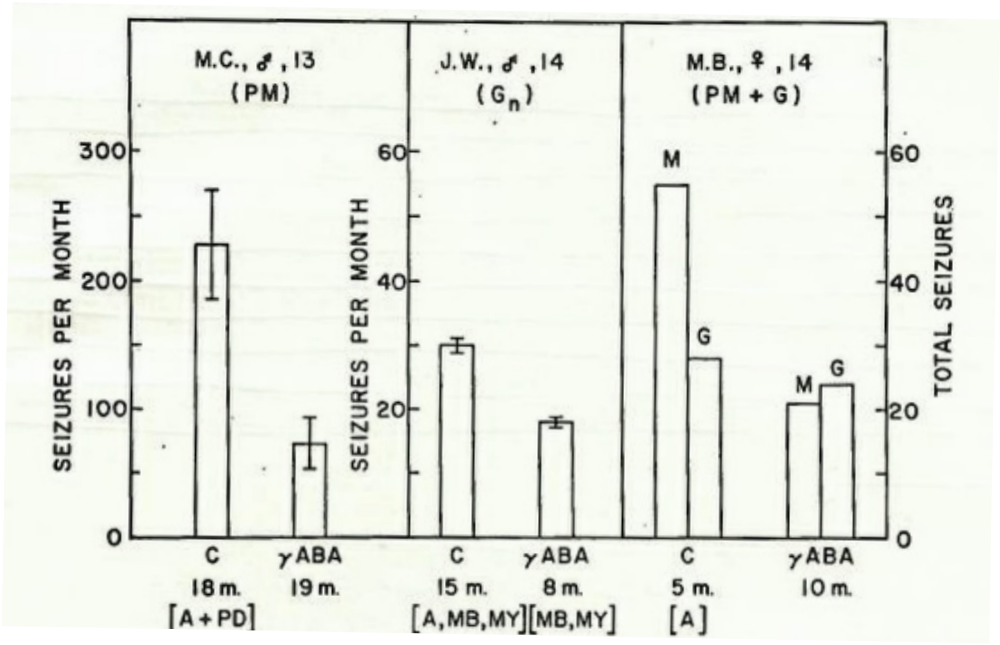
Figure 2. Electroencephalographic records of patient J. D. (Fig. 1) at the start of hyperventilation (samples on left) and at the end of 3 min of hyperventilation (sample on the right). Record A taken before second trial of GABA (see Fig. 1) when frequency of seizures was 200-300 per month. Record B taken at the end of month 18 (see Fig. 1) while on oral GABA 2mM/kg 4 times daily. Seizure frequency at this time was less than 40/month. Electrode placements, instrument calibrations and other conditions were the same for both recordings. Time and calibration scales given between lower records. Electrode leads given between upper records (abbreviations: R=right; L=left; F=frontal; C=central; P=parietal; O=occipital – all in the midlateral plane – T=temporal (ear); and V=mid-vertex) (Tower, 1960, p. 570). Reprinted with permission from: Tower, D. B. (1960). The administration of gamma-aminobutyric acid to man: Systemic effects and anticonvulsant action. In Inhibition in the nervous system and gamma-aminobutyric acid (pp. 562-578). New York, NY: Pergamon Press, Inc.



to ascertain the effects upon the frequency of seizures. Tower (1960) reported on a 14-year-old boy "with nocturnal generalized (or major) seizures" who also had a clinically significant reduction in seizure frequency when GABA was added to his anti-seizure medications - i.e., mephobarbital and mysoline (pp. 570-571). This patient's seizures always resulted in micturition, but with the reduction in seizure frequency from GABA his urination issue completely resolved. From looking at this case more closely, it appears that when the patient was treated with the anti-seizure medications listed above and L-asparagine for 15 months, the frequency of his seizures was around 30 per month, but once GABA was added (2 mM/kg 4 times daily) and L-asparagine discontinued, the frequency reduced to around 18 per month during 8 months of observation (**Figure 3,** below).

A third case (Tower, 1960) involved a 14-year-old girl with diagnoses of minor petit mal-type and major or generalized seizures. During 5 months on L-asparagine she was having around 280 minor or petit mal seizures each month, and around 150 generalized or major seizures each month. GABA was added (2 mM/kg 4 times daily) and she was followed for 10 months. During this observation period she was on no anti-

Figure 3. Seizure frequencies for three patients during control (C) periods and periods on oral GABA 2 mM/kg 4 times daily. Observation periods in months (m) indicated below each bar. For two patients on the left seizures are plotted as mean frequency per month for each period with the standard deviations indicated by the central line atop each bar. For patient M. B. on the right seizure are plotted as total number for the entire respective observation periods. (Abbreviations: Seizure types: PM= petit mal; Gn=nocturnal generalized or major; G=generalized or major; M=minor or petit mal; medications during control periods: A=L-asparagine; PD=paramethadione; MB=mephobarbital/Mebaral; MY=Mysoline). (Tower, 1960, p. 571). Reprinted with permission from: Tower, D. B. (1960). The administration of gamma-aminobutyric acid to man: Systemic effects and anticonvulsant action. In Inhibition in the nervous system and gamma-aminobutyric acid (pp. 562-578). New York, NY: Pergamon Press, Inc.



seizure medication, except for GABA, and the typical premenstrual spike in seizures diminished, the minor or petit mal seizures decreased to approximately 110 per month, and the generalized or major seizures to approximately 115 per month (**Figure 3**).

The fourth case (Tower, 1960) involved a 13-year-old boy with petit mal seizures. During 18 months on L-asparagine and paramethadione, he was having approximately 230 seizures each month. GABA was taken exclusively, and during the 19 month observation period, the frequency of seizures reduced to around 70 each month (**Figure 3**).

Based on the aforementioned results, Tower (1960) noted the following:

"These four patients demonstrate that daily oral administration of GABA can be an effective anticonvulsant, and it can appropriately prove effective against various different types of seizures. The seemingly readier response of the minor or petit mal types cannot properly be evaluated on such a limited number of patients (p.571)."

Tower (1960) also noted that there were other cases, however, where the use of GABA did not result in any reduction in seizure frequency. He described a 35-year-old man with petit mal-type seizures who took GABA for almost 2 years without any change in seizure frequency compared to an earlier control period when GABA was not taken. There was a 16-year-old girl with petit mal-type seizures primarily occurring with menstruation, who did not experience any clinically significant benefit from GABA over a 6 month period of observation. Regarding other patients who also underwent brief trials of GABA but did not respond, Tower commented:

"Regardless of factors perhaps peculiar to GABA, these differences in clinical response are not too surprising, since there is no known anticonvulsant which has proved effective in more than about two-thirds of a given epileptic population (p.572)."

GABA and Phosphatidylserine

A study evaluated supplemental GABA and phosphatidylserine (PS) among teenage and adult patients (age range: 15-65; n=42) with various forms of epilepsy (Loeb et al, 1987). These orthomolecules were used because anti-seizure activity was previously demonstrated when they were administered parenterally in a liposomal suspension in different seizure models, and when they were administered separately to rats. The oral forms of GABA and PS were studied because, as the authors' noted, they were readily available and shown to be safe for human consumption. Only 34 patients completed the study. All patients in this study were on 1-3 anti-seizure medications. There were three separate trials in the study, denoted as Trials A, B, and C.

Trial A (n=12) determined if combining anti-seizure medication with the supplements resulted in any alteration in the plasma levels of anti-seizure medication, with titrating doses of GABA (from 1,500-2,500 mg/day) and PS (from 300-500 mg/day). The results of Trial A did not demonstrate any statistically significant alteration in the plasma levels of anti-seizure medication.

Trial B (n=10) utilized a double-blind procedure in assessing the efficacy of the supplements (i.e., 2,500 mg/day GABA and 500 mg/day PS) over a treatment duration of 3 months.

Trial C utilized a single-blind procedure over a treatment duration of 8 months in assessing the efficacy of the supplements (i.e., 2,500 mg or 3,000 mg of GABA daily, either dose in combination with 500 mg/day PS). All patients in Trials B and C were considered to have responded when there was a 50% or more drop in the mean monthly seizure frequency compared to the respective reference periods and/or placebo periods.

The results (Loeb et al, 1987) showed significant clinical improvements, with 10 patients from the 34 (29.4%) having a demonstrable drop in seizure frequency (expressed as mean number of seizures per month ± SD) of 50% or more. When the results were analyzed more closely only the patients with AS showed statistically significant differences from the reference period and placebo, and clinically significant differences in monthly seizure frequency. A

total of 12 patients with AS were analyzed separately to determine their response to the supplements. With respect to Trial A (n=5 with AS), there was a clear dose-response relationship demonstrating a drop in seizure frequency with increasing doses of GABA and PS. When combining Trials B and C (n=7 with AS), there were statistically significant, as well as obvious clinical differences, between treatment versus the reference period, and treatment versus placebo. There were statistically significant decreases in the mean number of seizures per month when comparing the reference period (22±16) and placebo (16±12) to that of treatment (5±9). When Trials A, B, and C were combined (n=12 with AS), the results demonstrated a statistically significant drop in the mean numbers of seizures per month during the reference period (29±18) and treatment period (12±13).

Adverse effects were considered minimal and of no clinical concern (Loeb et al, 1987). Only 1 patient experienced significant gastric distress and dropped out, 2 patients experienced nausea, 4 patients had drowsiness, 1 with constipation, and 1 with a brief spell of amenorrhea. No changes in lab values were evident in 37 patients, but 5 did have minimal increases in alanine aminotransferase and decreases in fibrinogen and prothrombin time. The authors concluded that the combined use of GABA and PS "brought about a significant decrease in absence seizures, while complex partial seizures showed no significant changes" (pp.211-212). Even though the results were considered to be very preliminary, the authors mentioned that there is a rather urgent need to further study the therapeutic effects of GABA and PS among subjects having AS.

Another report on the combination of GABA and PS was published by Cocito, Bianchetti, Bossi, Giberti, and Loeb (1994). They investigated the anti-seizure properties of this combination in 9 patients with seizures associated "with an EEG pattern of photoconvulsive response at intermittent photic stimulation" (p. 49). They administered GABA (3,000 mg) and PS (600 or 1,200 mg) once orally, and then assessed for any changes that would suggest anti-seizure activity among the study subjects exposed to intermittent photic stimulation. They concluded that a single dose of this combination was ineffective, but that chronic administration may be required to demonstrate benefits. What was surprising about this study was that all the prior research related to seizures and GABA and/or PS had clearly demonstrated benefits only from chronic and not from acute administration. This study was not methodologically well constructed from the outset, and given the outcomes from previous research, there was little probability that the single-dose administration of the GABA-PS combination would demonstrate any significant clinical effects.

With respect to adverse effects from PS (those from GABA have already been discussed), PS has a tremendous safety record and produces rare stomach upset when large daily doses are used (e.g., 600 mg), or possibly sleeplessness if taken immediately before bed (Kidd, 1996). Otherwise, numerous clinical trials on more than 800 patients have shown PS to be very safe and well tolerated (Kidd, 1996).

Putative Mechanisms of Action

Based on the clinical data presented thus far, it is evident that GABA and the GABA-PS combination represents a novel complementary approach to the treatment of AS. With respect to how GABA exerts its therapeutic effects, Tower (1960) reported that there did not seem to be any strong connection between the reported therapeutic responses to GABA and its levels in the blood and cerebrospinal fluid. When commenting further, he noted that any "direct response between body fluid levels and therapeutic response should not necessarily be expected for a compound like GABA, which if it does penetrate from blood into the central nervous system, might pass directly to the tissues rather than into cerebrospinal fluid" (p.574). Lastly, he mentioned that given the possibility that epilepsy represents a condition associated with increased blood-brain-barrier

permeability, there is also the possibility of increased cerebral penetration of "systemically administered GABA" (p.575).

Modern research has attempted to better understand how GABA exerts its effects on the central nervous system. In a study (Abdou et al, 2006) that assessed GABA's effects upon relaxation and immunity, a mere 100 mg orally resulted in EEG changes associated with increased alpha waves and decreased beta waves among healthy volunteers. These effects were more significant than EEG alterations associated with water and L-theanine administration. These results suggested that GABA possesses anxiolytic and relaxation effects mediated by alterations in brain wave activity. In another study (Yoto et al, 2011) responses to mental stress was evaluated among healthy adults given 100 mg of GABA orally or placebo. GABA abrogated the drop in alpha and beta brain waves following mental stress. The subjects on placebo had more marked declines in their alpha and beta brain waves compared to the brain waves declines among the subjects taking GABA. Changes in the "vigor-activity" scores of the Profile for Mood States questionnaire among the subjects on GABA were less pronounced than those associated with placebo, which reflected a potential benefit upon mood or a subjective anti-stress effect from the orthomolecule.

A study among healthy human volunteers (Fujibayashi, Kamiya, Takagaki, and Moritani, 2008) demonstrated that following an overnight fast, the oral use of GABA (precise dose unspecified) resulted in increased autonomic nervous system and parasympathetic nervous system activity. While I was not able to read the actual study since it was published in Japanese, the abstract in English reported that these positive changes were attributed to alterations in heart rate variability.

Another study assessed GABA and Apocynum venetum leaf extract (AVLE) to assist with sleep among 16 subjects suspected as having some type of sleep disorder (Yamatsu et al, 2015). The subjects were either given GABA alone (100 mg), AVLE alone (50 mg), or GABA (100 mg) combined with AVLE (50 mg) 30 minutes prior to bed. EEG and other measurements were taken. GABA administration resulted in shortened sleep latency by 5.3 minutes (i.e., with a trend toward statistical significance), and also reduced non-REM sleep latency but these latter findings did not reach statistical significance. These results, according to the authors, "suggested that GABA had an effect to help people to fall asleep quickly and easily" (p. 184). The mechanism underlying these effects on sleep were attributed to GABA's role as an inhibitory neurotransmitter in the central nervous system.

In a review article, *Neurotransmitters as food supplements: The effects of GABA on brain and behavior,* the mechanism of GABA was thoroughly discussed and debated (Boonstra et al, 2015). The article mentioned the controversy about whether or not GABA crosses the blood-brain-barrier, and raised some important possibilities to account for GABA's observed therapeutic effects. First, there is a GABA-transporter in the blood-brain-barrier, which means that GABA enters or exits the brain through facilitated transport. Given the fact that in mice the influx rate was found to be much slower than the efflux rate, there is the possibility that in humans GABA gains entrance into the brain, but is quickly moved out because of the very high efflux rate. This would make it extremely difficult to measure the amount of GABA in the central nervous system following oral administration because of the very high efflux rate. Second, there is the possibility that GABA works better among younger individuals because some evidence suggests that blood-brain-barrier permeability reduces with age. So perhaps younger patients such as children and teenagers would respond better to GABA given their presumably more permeable blood-brain-barriers. Lastly, GABA might exert its effects indirectly via the enteric nervous system even though the relationship between "the oral administration of GABA, the vagal nerve and GABA levels in the brain has not been established yet" (p. 4).

With respect to PS, animal research has evaluated the effects of PS and GABA co-administration via parenteral routes. One report, for example, demonstrated that the acetylated

derivative of PS (i.e., lysophosphatidylserine; LS) possessed anticonvulsant effects against isoniazid-induced seizures in mice (Toffano, Mazzari, Zanotti, & Bruni, 1984). The anticonvulsant effect of LS was present in the absence of GABA, but was also shown to enhance the anticonvulsant effects of GABA when they were co-administered. In a rat study, both GABA and PS were found to possess no seizure activity when administered alone, but when co-administered they significantly reduced the number of spikes among rats with penicillin-induced seizures (Loeb et al, 1985). Another report on rats (Benassi et al, 1992) demonstrated that when PS was co-administered with GABA, there was a resultant increase in the synaptic availability of the neurotransmitter, thus increasing the supply to GABA-ergic nerve endings. These findings suggest that PS might possess anti-seizure effects on its own, but most likely augments the anti-seizure effects of GABA when they are co-administered. Ultimately, however, PS exerts broad-spectrum effects that influence nerve cell membrane functionality by optimizing a variety of homeostatic processes - such as the entry of micronutrients into neurons, and energy production by functioning as a metabolic backup to other phospholipids (Kidd, 1996).

Discussion

It is apparent that some patients with AS will benefit when GABA or GABA-PS are combined with standard anti-seizure medication. The earlier work on GABA used tremendous daily doses (0.8 g/kg) to achieve positive therapeutic effects. Such a high daily dose would likely be difficult for most patients to sustain over extended periods of time, and the monthly costs could be prohibitive. It appears that PS augments the anti-seizure effects of GABA, which allows for a much smaller daily dose of GABA without compromising clinical efficacy. This would be much easier to comply with over extended periods of time, and be more affordable. When reviewing all the clinical data, GABA and GABA-PS represent novel complementary approaches to the management of AS (formerly classified as petit mal seizures), and possibly other types of generalized seizures. **Table 2,** (p.111) contains a summary of all the published results, which clearly point to a very tolerable, safe, and potentially effective treatment.

Case: Six-Year-Old Girl with CAE

Sometime in January 2016, 6-year-old Victoria was having episodes where she would space out for several seconds at a time during the day. From January to March the parents simply thought their daughter was not paying attention, and often they would talk loudly to capture her attention once again. The mother noticed that in March the frequency where Victoria would space out became observably more numerous, and these spacing-out spells were happening upwards of 5 times each hour. Because the spacing out became more pronounced the mother inquired if Victoria's teachers at school noticed anything similar. The teachers did not report on anything unusual, but Victoria's good friend did tell the mother that she had noticed Victoria spacing out a lot. The mother and father did their own research and were convinced that Victoria had CAE. The mother tested their concern by yelling into Victoria's ear during one of the episodes to see if this would startle her, but there was no startle response. This more or less confirmed their suspicion that Victoria had CAE.

Shortly after, on April 8th, they took Victoria to see their family physician who could not confirm the diagnosis until a video EEG was done. They estimated at the appointment that Victoria was likely having upwards of 5 seizures each hour (sometimes less and sometimes more). Thus, Victoria was having approximately 40 seizures each day. Sometimes during a seizure she would just blink or lick her lips, and other times she might also walk a little or speak incoherently.

The video EEG done on April 16th confirmed the presences of seizures. The pediatric neurologist who interpreted the EEG stated the following in the "Impression" section of the report:

Table 2. Clinical response to GABA and GABA-PS among patients with absence seizures

Intervention	Daily dose	Clinical outcome
GABA	0.8 g/kg	Significant reduction in monthly seizure frequency among 4/11 patients (36%; Tower, 1960).
GABA-PS	3,000 mg GABA; 500mg PS	Reduction in monthly seizure frequency of 50% or more in 10/34 patients (29.4%); 12 patients with AS showed the most marked clinical response with a statistically significant drop in the mean number of seizures per month (29±18 during the reference period to 12±13 during the treatment period; Loeb et al, 1987).

"This routine awake video EEG is mildly abnormal with several paroxysms recorded of generalized 3/s spike and slow wave activity which were enhanced during hyperventilation and accompanied clinically by staring and unresponsiveness. There was also a prolonged event which could have been triggered by photic stimulation at 8 Hz. The overall findings are in keeping with primary generalized epilepsy and the more prolonged events recorded, with absence seizures. Clinical correlation is indicated."

On April 21st they had their first visit with the pediatric neurologist who correlated the video EEG with the history that the parents' reported and agreed that Victoria's primary diagnosis was CAE. Prior to the appointment, the father had done research and began giving Victoria GABA (3,000 mg/day) on April 17. He believed that there was a reduction (but not complete cessation) in her seizure activity. The wife, on the other hand, was not sure if the GABA lessened the frequency of seizures. The father brought the information about GABA to show the physician, but he dismissed the information and would not agree to even review it. The father stated that given the possible adverse effects of ES, why not combine it with GABA and even PS so that a smaller daily dose might be used? The physician again expressed no interest in the information and told the parents to begin with 3 ml (150 mg) twice daily, increasing over a 14-day period to 5 ml (250 mg) twice daily.

On April 22nd Victoria began the ES at the 3 ml twice daily dosage along with 1,500 mg GABA twice daily, and a liquid fish oil product - that contained 100 mg PS, 350 mg docosahexaenoic acid (DHA), 150 mg eicosapentaenoic acid (EPA), 1,000 IU vitamin D3, 2 mg lutein, and 1 mg zeaxanthin per 5 mL - given twice daily with the GABA. She also continued with a chewable multiple vitamin/mineral supplement that she had taken since she was a toddler, along with 500 mg or more of vitamin C several times each week. Prior to using the liquid fish oil that contained PS, Victoria had taken a teaspoon daily of a different product that provided 320 mg EPA, 200 DHA, and 50 mg gamma-linolenic acid (GLA).

Victoria has been on 300 mg ES, 3,000 mg GABA, and 200 mg PS for more than

seven months. The parents have not seen even one absence seizure or a hint a seizure activity since commencing treatment with this combination. Victoria has not had any problems tolerating the treatments, is now 7 years old, and thankfully there has not been any need to increase the daily dose of ES thus far. Compliance has not been much of an issue. At first, Victoria consumed the GABA mixed in applesauce, but has since learned how to swallow pills, and now swallows the GABA (2 x 750 mg) twice daily without any problems. She has become much more engaged and focussed since receiving treatment, and she has been less shy and more sociable at school. She is thriving and doing well overall. Victoria will be getting another video EEG when she has been seizure-free for 2 years, at which point the ES will be gradually discontinued to ascertain if she still needs it.

It should be noted that in the study cited earlier (Glauser et al, 2010) that involved patients with new onset CAE, the mean dose of ES at final evaluation was 33.5±15.3 mg/kg of body weight, with 17.5% of the group requiring the maximal dose of medication (2,000 mg/day). The trial duration was 16 to 20 weeks, and only 53% of patients taking ES became seizure-free. Victoria, on the other hand, had an immediate remission in all seizure activity with this combination, and has maintained the same daily dose of ES for more than 7 months (300 mg) without needing an increase. According to the mean daily dose from the study, Victoria should be taking approximately 670 mg (based on her 20 kg weight) to be free from seizures. It is possible that she has only responded to the ES and not the other treatments. However, given how common and usually necessary it is for doses of anti-seizure medication to be increased - including the fact that the father noticed a reduction in seizure activity while taking GABA prior to instituting anti-seizure medication - it does seem possible and likely that the combination of ES, GABA, and PS has produced the very favourable outcome to date. This combination approach has kept Victoria's daily dose of ES low, and she has not experienced any concerning adverse effects.

Addendum to an Earlier Report

Previously, I reported on the integration of several orthomolecules - i.e., chromium, GABA, magnesium, manganese, taurine, vitamins B_3 and B_6, and zinc - with anti-seizure medication, and suggested that this approach facilities "noteworthy quality of life enhancements" by reducing the frequency and intensity of seizure activity (Prousky, 2014, p.168). I also presented several cases documenting the putative efficacy of this approach.

One of the cases involved a pediatric patient with MRI results suggestive of focal cortical dysplasia, which results from some type of malformation of cortical development causing symptomatic focal epilepsy in childhood and even adulthood (Fauser, 2006). The patient was initially seen in my private clinical practice on November 2012, when she was having nighttime seizures with a seizure frequency of approximately one every 2 months. She was not on anti-seizure medication when I began working with her. She was put on a plan that involved the following regimen: vitamin C (500 mg twice daily); omega-3 essential fatty acids (1 teaspoon daily providing 320 mg of EPA, 200 mg of DHA, and 50 mg of GLA); vitamin B_6 (100 mg twice daily); magnesium-taurine (providing 200 mg of magnesium and 600 mg of taurine daily); and GABA (200 mg at bedtime). At subsequent visits the daily dose of GABA was increased to 400 mg at bedtime, and the magnesium-taurine was increased such that the daily intake provided 300 mg of magnesium and 900 mg of taurine. The patient experienced approximately 13 seizures in total as documented in a report from her pediatric neurologist (dated: July 8, 2014) who identified that the patient had remained clinically free of seizures since September 2013. The most recent video EEG (dated: June 18, 2014) showed an absence of seizure activity during the awake and sleep period. I have continued to follow this patient's progress closely. She has remained seizure-free on the orthomolecular approach for approximately 26 months (last update with patient's father: November 11, 2016), and has not needed any anti-seizure medica-

tion. She has a video EEG planned sometime in December 2016. Her current treatment plan has remained essentially the same during this duration, except that the magnesium-taurine compound changed, and now provides less magnesium (195 mg/day), but the same amount of taurine (900 mg/day).

Given the favourable response as described in this case, as well as other positive responses documented in my 2014 paper, I believe that all patients with epilepsy would potentially benefit from a regimen of orthomolecules in combination with anti-seizure medication. Thus, it makes sense to consider a transdiagnostic approach to epilepsy that would encompass many of the micronutrients that appear to lessen seizure frequency and intensity, and promote a better quality of life. **Table 3** (p.114) lists the therapeutic dose ranges, based on published sources (for more specific references, see Prousky, 2014) and my clinical experience, of all the orthomolecules that could be given to patients with epilepsy to improve outcomes, especially because it can be difficult to control the activity of seizures among medicated patients that have remained treatment resistant. PS was added to the list based on the information presented in this report.

Vitamin D3 was also added because a pilot study by Holló, Clemens, Kamondi, Lakatos, and Szucs (2012) demonstrated a median seizure reduction of 40% in 10 of 13 patients with various types of epilepsy from supplementation. All the patients in the study were adults with a disease duration ranging from 10 to 42 years, and all were considered to be pharmacoresistant. When the deficient 25(OH)D levels (defined as <30 ng/mL or <75 nmol/L) were normalized from vitamin D3 supplementation, 10 patients experienced decreased seizure frequency during the 90-day observation period, with 5 having a marked seizure reduction of ≥50%. The precise mechanism of action for vitamin D3 and how it moderates seizure frequency is not well known, but vitamin D receptors and the enzyme that produces its active form are widely found in the brain (Eyles, Smith, Kinobe, Hewison, & Mcgrath, 2005). Vitamin D might also exert its effect in the central nervous system via calcemic and non-calcemic actions (Stewart et al, 2010). Gene expression from vitamin D is also altered when activated by the binding of 1,25(OH)D to the nuclear vitamin D receptor (Ramagopalan et al, 2010).

With respect to vitamin B_3, here I have included details that were not reported in my prior publication (Prousky, 2014). Hoffer (1962) reported that niacin (nicotinic acid) can reduce the amount of anti-seizure medication needed while still affording adequate seizure control. Here is a passage from Hoffer's report noting the beneficial effects from 3 g of niacin:

"I have given nicotinic acid at this dosage to six epileptics who were having difficulty with control. When they were given sufficient anticonvulsants to control the convulsions they were much too sedated and were ineffective at their jobs, etc. When they were given 3 grams nicotinic acid per day the amount of anticonvulsant could as a rule be halved. One male epileptic needed 800 mg of mesantoin daily to be free of fits, but this large dose made him too sluggish and dopey to do his work. Three grams of nicotinic acid daily allowed me to reduce his dose of mesantoin to 200 mg, yet remain free of seizures, be normally alert and keep his job. He remained on this combination for years (p. 25)."

Hoffer (1962) also cited a case in more detail describing the therapeutic effects of vitamin B_3 (as niacinamide) in a 16-year-old female having a history of mixed petit mal and grand mal seizures, taking phenobarbital and dilantin to control them. When she was examined, it was apparent that her daily doses of anti-seizure medication (i.e., 300 mg dilantin and 90 mg phenobarbital) were causing symptoms of over-sedation, which made it likely that she would lose her job because of making too many mistakes. She also exhibited perceptual changes that included laughing frequently and inappropriately. Hoffer commented that the "problem was to provide a balance between freedom from convulsions and freedom from over sedation" (p. 28). He started her on 3 g of niacinamide

daily, and reduced the dilantin to 160 mg and the phenobarbital to 60 mg. She was seen a little over 6 months later, did not report any seizures, had no more perceptual changes, and demonstrated good cognition and mood during the examination. A little less than 3 months later, she continued to be free from seizures, and was looking forward to pursuing a Bachelor of Arts degree at university.

Other data cited by Hoffer (1962) showed that children given doses of niacin as low as 50 mg orally had EEG changes within 5 to 10 minutes whereby the vitamin "produced a dramatic normalization of high voltage alpha activity without spiking" (p. 28). He further remarked that while niacin and niacinamide produce EEG effects similar to that of barbiturates, they do not impair consciousness or awareness, but in fact "they calm and tranquilize without lessening awareness" (p. 29). As I suggested in my prior publication (Prousky, 2014), niacinamide is preferred because the cutaneous flushing seldom happens, and because this form of vitamin B_3 influences the GABA system, and has therapeutic effects similar to that of benzodiazepine medications commonly used to suppress seizure activity.

This approach should be combined with a multiple vitamin/mineral supplement to ensure that the minimum requirements are met for all the essential micronutrients. More study is certainly needed, but given the fact that uncontrolled or treatment-resistant epilepsy is potentially life threatening and definitely life impairing, I cannot think of any justifiable reason to withhold this approach given the potential upside, and the relative long-term safety and tolerability of these commonly-consumed orthomolecules.

Conclusion

This report focussed on CAE, but also included information relevant to adults with AS as well as other types of seizures. While some children with CAE will grow out of their seizures (i.e., remit) within 2-5 years of onset (Panayiotopoulos, 1999), some children experience persistent seizures into adulthood, and some have seizures that evolve into the generalized tonic-clonic type. Because pharmacoresistance is a real and known concern - and because some patients with CAE have

Table 3. Transdiagnostic orthomolecular approach to epilepsy 1.0

Intervention	Suggested daily therapeutic dose range
Chromium picolinate	200-600 mcg (in suspected hypoglycemia-associated seizures)
GABA	400-3,000 mg
Magnesium	200-600 mg (or more aggressively, 5-30 mg/kg)
Manganese	15-30 mg
Phosphatidylserine	200-500 mg
Taurine	100-1,500 mg (or more aggressively, up to 8,000 mg)
Vitamin B3	500-2,500 mg (as niacinamide)
Vitamin B6	60-200 mg (consider pyridoxal phosphate - the more potent form - at a dose of 7-38 mg/kg)
Vitamin D3	Optimal daily doses to maintain a 25(OH)D] level ≥30 ng/mL (≥75 nmol/L)
Zinc	10-80 mg (consider adding 1-2 mg of copper if high doses of zinc, i.e., at or above 80 mg are taken long-term)

persistent epilepsy into adulthood - it behooves all clinicians to think outside of the box and consider augmenting anti-seizure medication with dietary interventions (e.g., the KD, MAD, or Paleolithic KD), or with specific orthomolecules, such as GABA and PS. For patients with related or different types of seizures, I also proposed a transdiagnostic orthomolecular approach that could be offered in conjunction with anti-seizure medication to lessen seizure frequency and improve quality of life. Once again, it behooves all clinicians to consider several or all of the transdiagnostic orthomolecular treatments when faced with epilepsy patients that have remained treatment resistant, and have experienced repeated seizures with debilitating and potentially life-threatening effects on their quality of life.

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Competing Interests

The author declares that he has no competing interests.

Statement of Informed Consent

Written consent was obtained from the guardians of the patients described in this report.

References

Abdou, A. M., Higashiguchi, S., Horie, K., Kim, M., Hatta, H., & Yokogoshi, H. (2006). Relaxation and immunity enhancement effects of Gamma-Aminobutyric acid (GABA) administration in humans. *BioFactors,* 26(3), 201-208.

Banich, M.T., & Compton, R.J. (2013). Generalized cognitive disorders. In *Cognitive Neuroscience* (3rd ed., Int ed., pp. 466-497). United Kingdom: Wadsworth Cengage Learning.

Benassi, E., Besio, G., Cupello, A., Mainardi, P., Patrone, A., Rapallino, M. V., . . . Loeb, C. W. (1992). Evaluation of the mechanisms by which gamma-amino-butyric acid in association with phosphatidylserine exerts an antiepileptic effect in the rat. *Neurochemical Research,* 17(12), 1229-1233.

Berg, A. T., Shinnar, S., Levy, S. R., Testa, F. M., Smith-Rapaport, S., & Beckerman, B. (2000, 10). How Well Can Epilepsy Syndromes Be Identified at Diagnosis? A Reassessment 2 Years After Initial Diagnosis. *Epilepsia,* 41(10), 1269-1275.

Boonstra, E., Kleijn, R. D., Colzato, L. S., Alkemade, A., Forstmann, B. U., & Nieuwenhuis, S. (2015). Neurotransmitters as food supplements: The effects of GABA on brain and behavior. *Frontiers in Psychology,* 6, 1-6.

Bouma, P., Westendorp, R. G., Dijk, J. G., Peters, A. C., & Brouwer, O. F. (1996). The outcome of absence epilepsy: A meta-analysis. *Neurology,* 47(3), 802-808.

Clemens, Z., Kelemen, A., Fogarasi, A., & Toth, C. (2013). Childhood absence epilepsy successfully treated with the Paleolithic ketogenic diet. *Neurology and Therapy,* 2(1), 71-76.

Cocito, L., Bianchetti, A., Bossi, L., Gilberti, L., & Loeb, C. (1994). GABA and phosphatidylserine in human photosensitivity: A pilot study. *Epilepsy Research,* 17(1), 49-53.

Engelborgh, S., D'Hooge, R., & De Deyn, P. P. (2000). Pathophysiology of epilepsy. *Acta Neurologica Belgica,* 100(4), 201-214.

Eyles, D. W., Smith, S., Kinobe, R., Hewison, M., & Mcgrath, J. J. (2005). Distribution of the Vitamin D receptor and 1?-hydroxylase in human brain. *Journal of Chemical Neuroanatomy,* 29(1), 21-30.

Fauser, S., Huppertz, H-J., Bast, T., Strobl, K., Pantazis, G., Altenmueller, D-M., … Schulze-Bonhage, A. (2006). Clinical characteristics in focal cortical dysplasia: A retrospective evaluation in a series of 120 patients. *Brain,* 129(7), 1907-1916.

Fujibayashi, M., Kamiya, T., Takagaki, K., & Moritani, T. (2008). Activation of Autonomic Nervous System Activity by the Oral Ingestion of GABA. *Journal of Japan Society of Nutrition and Food Science,* 61(3), 129-133.

Glauser, T. A., Cnaan, A., Shinnar, S., Hirtz, D. G., Dlugos, D., … Adamson, P. C [on behalf of the Childhood Absence Epilepsy Study Group]. (2010). Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *New England Journal of Medicine,* 362(9), 790-799.

Groomes, L. B., Pyzik, P. L., Turner, Z., Dorward, J. L., Goode, V. H., & Kossoff, E. H. (2011). Do patients with absence epilepsy respond to ketogenic diets? *Journal of Child Neurology,* 26(2), 160-165.

Hoffer, A. (1962). *Niacin therapy in Psychiatry.* Springfield, IL: Charles C Thomas.

Holló, A., Clemens, Z., Kamondi, A., Lakatos, P., & Sz?cs, A. (2012). Correction of vitamin D deficiency improves seizure control in epilepsy: A pilot study. *Epilepsy & Behavior,* 24(1), 131-133.

Jallon, P., Loiseau, P., & Loiseau, J. (2001, 12). Newly diagnosed unprovoked epileptic seizures: Presentation at diagnosis in CAROLE study. *Epilepsia,* 42(4), 464-475.

Kidd, P. M. (1996). Phosphatidylserine: Membrane nutrient for memory. A clinical and mechanistic assessment. *Alternative Medicine Review,* 1(2), 70-84.

Kossoff, E. H., Cervenka, M. C., Henry, B. J., Haney, C. A., & Turner, Z. (2013). A decade of the

modified Atkins diet (2003-2013): Results, insights, and future directions. *Epilepsy & Behavior,* 29(2013), 437-442.

Kossoff, E. H., Mcgrogan, J. R., Bluml, R. M., Pillas, D. J., Rubenstein, J. E., & Vining, E. P. (2006). A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. *Epilepsia,* 47(2), 421-424.

Kossoff, E. H., Zupec-Kania, B. A., & Rho, J. M. (2009). Ketogenic diets: An update for child neurologists. *Journal of Child Neurology,* 24(8), 979-988.

Li, J., Zhang, Z., Liu, X., Wang, Y., Mao, F., Mao, J., . . . Wang, Q. (2015). Study of GABA in Healthy Volunteers: Pharmacokinetics and Pharmacodynamics. *Frontiers in Pharmacology,* 6, 1-9.

Loeb, C., Benassi, E., Bo, G. P., Cocito, L., Maffini, M., & Scotto, P. (1987). Preliminary investigation of the effect of GABA and phosphatidylserine in epileptic patients. *Epilepsy Research,* 1(3), 209-212.

Loeb, C., Bo, G. P., Scotto, P. A., Benassi, E., Besio, G., Mainardi, P., & Faverio, A. (1985). GABA and phospholipids in penicillin-induced seizures. *Experimental Neurology,* 90(1), 278-280.

Loiseau, P., Duche, B., & Pedespan, J. (1995). Absence epilepsies. *Epilepsia,* 36(12), 1182-1186.

Panayiotopoulos, C. P. (1999). Typical absence seizures and their treatment. *Archives of Disease in Childhood,* 81(4), 351-355.

Pavone, P., Bianchini, R., Trifiletti, R., Incorpora, G., Pavone, A., & Parano, E. (2001). Neuropsychological assessment in children with absence epilepsy. *Neurology,* 56(8), 1047-1051.

Proposal for revised classification of epilepsies and epileptic syndromes. (1989). *Epilepsia,*30(4), 389-399.

Prousky, J. E. (2014). The adjunctive treatment of epilepsy with orthomolecular substances. *Journal of Orthomolecular Medicine,* 29(4), 167-175.

Ramagopalan, S. V., Heger, A., Berlanga, A. J., Maugeri, N. J., Lincoln, M. R., Burrell, A., . . . Knight, J. C. (2010, 08). A ChIP-seq defined genome-wide map of vitamin D receptor binding: Associations with disease and evolution. *Genome Research*, 20(10), 1352-1360.

Sharma, S., & Jain, P. (2014). The modified atkins diet in refractory epilepsy. *Epilepsy Research and Treatment,* 2014, 1-6.

Sillanpää, M., & Shinnar, S. (2010). Long-Term Mortality in Childhood-Onset Epilepsy. *New England Journal of Medicine,* 363(26), 2522-2529.

Stewart, A., Wong, K., Cachat, J., Elegante, M., Gilder, T., Mohnot, S., . . . Kalueff, A. V. (2010). Neurosteroid vitamin D system as a nontraditional drug target in neuropsychopharmacology. *Behavioural Pharmacology,* 21(5-6), 420-426.

Toffano, G., Mazzari, S., Zanotti, A., & Bruni, A. (1984). Synergistic effect of phosphatidylserine with gamma-aminobutyric acid in antagonizing the isoniazid-induced convulsions in mice. *Neurochemical Research,* 9(8), 1065-1073.

Tower, D. B. (1960). The administration of gamma-aminobutyric acid to man: Systemic effects and anticonvulsant action. In *Inhibition in the Nervous System and Gamma-Aminobutyric Acid* (pp. 562-578). New York, NY: Pergamon Press, Inc.

Vega, C., Guo, J., Killory, B., Danielson, N., Vestal, M., Berman, R., . . . Spann, M. N. (2011). Symptoms of anxiety and depression in childhood absence epilepsy. *Epilepsia,* 52(8), 1528-1167.

Wahab, A. (2010). Difficulties in treatment and management of epilepsy and challenges in new drug development. *Pharmaceuticals,* 3(7), 2090-2110.

Wheless, J. W., Clarke, D. F., & Carpenter, D. (2005). Treatment of pediatric epilepsy: Expert opinion. *Journal of Child Neurology,* 20(Suppl 1), S1-S56.

Wirrell, E. C., Camfield, C. S., Camfield, P. R., Dooley, J. M., Gordon, K. E., Smith, B. (1997). Long-term psychosocial outcome in typical absence epilepsy: Sometimes a wolf in sheeps' clothing. *Archives of Pediatrics & Adolescent Medicine*,151(2), 152-158.

Yamatsu, A., Yamashita, Y., Maru, I., Yang, J., Tatsuzaki, J., & Kim, M. (2015). The improvement of sleep by oral intake of GABA and Apocynum venetum leaf extract. *Journal of Nutritional Science and Vitaminology,* 61(2), 182-187.

Yoto, A., Murao, S., Motoki, M., Yokoyama, Y., Horie, N., Takeshima, K., ... Yokogoshi, H. (2011). Oral intake of ?-aminobutyric acid affects mood and activities of central nervous system during stressed condition induced by mental tasks. *Amino Acids,* 43(3), 1331-1337.