The Adjunctive Treatment of Epilepsy with Orthomolecular Substances

Jonathan E. Prousky, ND, MSc[1,2]

1. Chief Naturopathic Medical Officer, Professor, Canadian College of Naturopathic Medicine, 1255 Sheppard Avenue East, Toronto, Ontario, M2K 1E2 email: jprousky@ccnm.edu; website: www.jonathanprouskynd.com
2. Editor, Journal of Orthomolecular Medicine, email: editor@orthomed.org

Abstract *Epilepsy can be understood as a disorder of abnormal brain electrical activity resulting in recurrent seizures. Underlying the abnormal brain activity are defects in gamma-aminobutyric acid (GABA) activity, GABA receptor inhibition, and even defects in the intracellular buffering of calcium. The mechanisms underlying the increased excitation include increased activation of N-methyl-D-aspartate receptors (NMDARs) and other processes. This article describes specific orthomolecules that possess anti-seizure activity by either up-regulating the GABA system and/or down-regulating the NMDAR system. Several patient cases are highlighted to show the potential benefits from this approach. Some case management tips are provided to assist clinicians in understanding how to implement this approach with their patients. Given how safe and cost-effective the orthomolecular approach is, this article asserts that the use of specific orthomolecules should be considered when patients (after having made an informed decision) want to complement their anticonvulsant medication, seek an alternative to anticonvulsant medication, or have not responded adequately to their anticonvulsant medications.*

Introduction

Epilepsy can be understood as a disorder of abnormal brain electrical activity resulting in recurrent seizures. It is diagnosed as a neurological disorder when there has been two unprovoked seizures.[1] Seizures result in clinical signs or symptoms that depend on "the extent and pattern of the propagation of the epileptic discharge in the brain."[1] Some possible causes of seizures include genetic predisposition, trauma, cerebrovascular accident, brain tumours, alcohol and drug withdrawal, and other conditions.

Brief Overview of Pathophysiology

In the cerebral cortex a network of cortical neurons can manifest seizure activity when "a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons in favour of a sudden-onset net excitation."[1] When the visual cortex is affected, visual manifestations can result. Other clinical manifestations (auditory, taste, and motor symptoms) can arise when the affected cortical network gets disrupted in specific sensory, gustatory, or motor areas.

The genesis of seizures arises from complex biochemical processes of reduced inhibitory activity and increased excitatory activity.[1] Underlying the abnormal cortical activity and decreased inhibition are defects in gamma-aminobutyric acid (GABA) activity, GABA receptor inhibition, and even defects in the intracellular buffering of

calcium. The mechanisms underlying the increased excitation include increased activation of N-methyl-D-aspartate receptors (NMDARs) and other processes.

Diagnostic Considerations

Referral to a neurologist is necessary in the evaluation of a patient suspected of having epilepsy. Serum prolactin levels can be elevated 3- or 4-fold following a seizure, but this only has relevance in generalized tonic-clonic seizures compared to other types.[1] To firmly establish a diagnosis, the neurologist will need to do two neuroimaging studies (e.g., head computed tomography/CT scan and brain magnetic resonance imaging/MRI) to assess for structural abnormalities, and electroencephalography (EEG) to assess for interictal epileptiform discharges or focal abnormalities.[1]

Orthomolecular Therapeutics

The epileptic patients who have sought out treatment from me have tended not to respond adequately to their anticonvulsant medications or do not want to take medications at all. I have seen many such patients report fewer seizures and less intense seizure activity when orthomolecules* were added to their existing anticonvulsant medication. I have also treated a handful of patients who chose not to take anticonvulsant medication. One such paediatric patient has remained seizure-free for more than 13 months. An adult patient remained seizure-free for eight months and then I lost contact with him. Another patient remained seizure-free for almost five months before we decided that the more appropriate path was to pursue anticonvulsant medication. Thus, I have observed some intriguing responses from orthomolecular treatments, and as a result, I am convinced that a number of orthomolecules possess anti-seizure properties that can facilitate noteworthy quality of life enhancements.

* The term, Orthomolecule, refers to substances found naturally or normally in the human body, such as amino acids, essential fatty acids, hormones, minerals, and vitamins.

Vitamin B_6

It is important to distinguish whether vitamin B_6 is given to guard against a deficiency, or is given to treat non-vitamin B_6-dependent epilepsy. I will not address vitamin B_6-dependent epilepsy since these usually occur within months of birth and can be controlled rather well with large supplemental doses of vitamin B_6.[2] Deficiency of vitamin B_6 is usually associated with the use of phenytoin.[3]

Three studies have shown that patients with epilepsy being treated with phenytoin are vulnerable to vitamin B_6 deficiency.[3-5] Some studies have shown supplemental vitamin B_6 to help with non- vitamin B_6-dependent epilepsy. In one study, 26 patients were given 160 mg/day of vitamin B_6.[6] Of the 26 patients, 19 were identified as having vitamin B_6 deficiency per an abnormal tryptophan load test. Nine of the patients had a complete (no seizure activity) or partial response (less seizure activity) to the vitamin, and some of these patients were able to discontinue their anticonvulsant medication. In another study, vitamin B_6 (20 mg 3-6 times/day) was given to 14 patients between 2 and 17 years of age.[7] Five patients had a complete response while three patients had a partial response to the vitamin. All of the patients in this study suffered from petit mal seizures, and one of the patients also had grand mal epilepsy. There are other positive studies and even some negative ones where vitamin B_6 did not help and actually worsened the clinical outcome. For a thorough review of many of the studies on vitamin B_6, please see Gaby.[8]

Dosage: To prevent deficiency of the vitamin for patients on phenytoin, Gaby recommends a daily dose of 10-50 mg. When using larger doses, Gaby recommends caution since high-dose vitamin B_6 can interfere with some anticonvulsant medications. He advises clinicians to add supplemental magnesium since vitamin B_6 increases the requirement for magnesium. The therapeutic range for vitamin B_6 is 60-200 mg/day, although higher daily doses might sometimes be needed.

The active form of vitamin B_6 (pyridoxal

phosphate/PLP) is more potent than regular vitamin B_6 as pyridoxine hydrochloride. I recommend that PLP be tried initially. The therapeutic dose of PLP should be in the range of 7-38 mg/kg/day.[8] For both forms of vitamin B_6, especially at high doses, watch for signs of toxicity (albeit, rare) such as peripheral neuropathy, central nervous system toxicity, elevated liver enzymes, and nausea and vomiting.

GABA

This amino acid functions as an inhibitory neurotransmitter. There are two forms of GABA available: crystalline GABA and PharmaGABA® (produced by a fermentation process that utilizes *Lactobacillus hilgardi*i).[9] Both forms have the same molecular structure and mechanism of action, and therefore it is unscientific to contend that one form somehow traverses the blood-brain barrier while another form does not.[10]

PharmaGABA® has been shown to favourably moderate various biochemical markers of stress.[9] In a study (n=13) that evaluated the therapeutic effects of PharmaGABA®, 60 minutes after ingesting 100 mg, the electroencephalographic readings showed statistically significant increases in alpha waves ($p<0.05$) and decreases in beta waves compared to results obtained when the same subjects were administered L-theanine and water.[11] Since these results showed PharmaGABA® to possess relaxation and anti-anxiety effects by increasing the production of alpha waves, this might be how it potentially moderates seizure activity.

Crystalline GABA has been given orally in certain cases of status epilepticus and has been effective.[12] One major study of crystalline GABA and vitamin B_6, as cited by Braverman et al, was purported to show improvement in 50% of the 699 epileptics given these supplements.[12] After having fully reviewed the original study[13] cited by Braverman et al, I have not been able to confirm that a human study involving 699 subjects actually took place. Thus, it is my opinion that Braverman et al either referenced the wrong study in their book, or they simply did not read the actual study they cited.

Dosage: I prefer the PharmaGABA® form based on my own empirical observations. The crystalline form usually comes in much higher doses per pill, such as 500 mg or 600 mg, and these doses now seem unnecessary. Crystalline GABA in doses of 1 to 3 grams per day might cause neurologic tingling and a flushing sensation.[12] I have found that 200-400 mg per day of PharmaGABA® produces anti-seizure effects when administered at bedtime, or even in the morning before breakfast. I have not observed any side effects from PharmaGABA®. The PharmaGABA® preparation has been tested in rats that were administered doses of 5,000 mg/kg.[9] There were no deaths and the LD50 was determined to be >5,000 mg/kg.

Taurine

The anti-seizure effects are probably the result of its membrane-stabilizing properties (it appears to normalize the flow of sodium, potassium, and calcium into and out of the cell).[14] Taurine might also help decrease seizure activity by lowering glutamic acid levels through the enhancement of glutamic acid decarboxylase.[14]

Dosage: According to Gaby, taurine has been administered orally and intravenously at doses ranging from 200 mg/day to 21 g/day.[8] The standard therapeutic dose is between 100 and 500 mg/day, even though 1.5 g/day was shown to induce anti-seizure activity in some patients in a published report.[8] The effective dose in rats is equivalent to 3.5-7 g/day in a 70 kg man, but doses in this range and even above 500 mg/day might cause amino acid imbalances and render this treatment ineffective.[8,15]

In a review article on the therapeutic applications of taurine, Birdsall noted that various trials have used between 375-8,000 mg/day providing outcomes with an efficacy somewhere between 16-90%.[16] Birdsall believes Taurine's dubious efficacy is the result of its "limited diffusibility across the blood-brain barrier," which may limit this amino acid from having strong anti-seizure effects.[16] My clinical experiences with taurine

have been positive. I have not observed any toxicity and have been unable to ascertain if it actually does lead to concerning amino acid imbalances when used for more than a couple of months.

Magnesium

Pfeiffer reported that a magnesium deficiency induces muscle tremors, depression, irritability, and occasionally convulsive seizures.[17] He cited the work of the late Adelle Davis who reported success in controlling seizure activity with 450 mg/day of magnesium, which apparently allowed patients to discontinue their anticonvulsant medications. Elevated N-methyl-D-aspartate and its metabolites can produce experimental seizures. Magnesium is a natural inhibitor of N-methyl-D-aspartate, and should be used to treat patients having both epilepsy and elevated levels of these compounds in their blood.[18] Some research has confirmed Pfeiffer's observations, in that magnesium depletion can both cause and increase seizure activity in response to seizure-inducing stimuli.[18,19] There is also data demonstrating lower levels of magnesium in both the serum and cerebrospinal fluid among patients with grand mal epilepsy compared to controls.[20,21]

Dosage: For optimal dosing of magnesium, patients should be given 5-30 mg/kg/day.

Case 1: Paediatric patient with MRI results suggestive of focal cortical dysplasia

This 7-year old patient presented to my private clinical practice (Toronto, Ontario) in November 2012. The first seizure occurred when she was six years old. The video EEG (June 2011) results during the awake and drowsy states demonstrated very active epileptiform spike slow wave discharges with an associated slow wave abnormality arising from the right posterior temporal region with infrequent spread into the left posterior temporal region. The subsequent MRI showed brain abnormalities suggestive of focal cortical dysplasia. At my initial evaluation, the patient's parents reported seven seizures in the preceding 16 months. They all happened at night. The patient also had a history of recurrent streptococcal pharyngitis, accompanied by chronically enlarged tonsils.

The parents wanted to try an orthomolecular approach since their daughter was unable to tolerate anticonvulsant medication due to an allergic reaction to carbamazepine and intolerant side effects from divalproex sodium. I prescribed the following: vitamin C (500 mg twice daily); omega-3 essential fatty acids (one teaspoon daily providing 320 mg of eicosapentaenoic acid, 200 mg of docosahexaenoic acid, and 50 mg of gamma-linolenic acid); vitamin B_6 (100 mg twice daily); magnesium-taurine (providing 200 mg of magnesium and 600 mg of taurine daily); and PharmaGABA® (200 mg at bedtime).

At the second visit (February 2013), the parents reported that the patient had a seizure in early December, but none since. They also had their daughter scheduled for tonsillectomy in March 2012. I increased the magnesium-taurine combination to three pills daily (providing 300 mg of magnesium and 900 mg of taurine).

At the third visit (August 2013), the parents reported that the surgery went well without incident. Their daughter had two seizures since the prior appointment (one in May and another in early August). I increased the PharmaGABA® to 400 mg at bedtime until the next follow-up.

At the forth visit (December 2013), the parents reported only one seizure since the last visit that happened in September. They noted results from the orthomolecular approach and were pleased with its absence of sedating effects.

At the most recent visit (November 2014), the parents reported that their daughter has been seizure-free since September 2013, approximately 13-14 months. They have seen their neurologist who was delighted with this news and told them to remain on the orthomolecular plan unless another seizure should occur.

The latest video EEG (June 2014) did not show any EEG seizures during the awake and sleep period. This patient is now 10 years old and enjoys her life, does well in

school, and barely thinks about the seizures that once consumed her life.

Her plan was modified to the following: magnesium-taurine (provides 130 mg of magnesium and 600 mg of taurine daily); vitamin B_6 (200 mg daily); PharmaGABA® (400 mg at bedtime); and the recommendation to continue with the same dosages of omega-3 essential fatty acids and vitamin C (as described previously).

Manganese

This trace mineral plays a significant role in cerebral metabolism and performs several physiological functions that include: (1) being a critical cofactor for glucose utilization within the neuron; (2) increasing adenylate cyclase activity (converts ATP --> cAMP); and (3) neurotransmitter control.[22] Like magnesium, there are studies demonstrating that patients with epilepsy have lower whole-blood manganese levels (20-41% lower) compared to controls.[23-28]

Dosage: The adult dose of manganese to control seizures is 15-30 mg/day, and it has a low level of toxicity.[22]

Zinc

Seizures might result when zinc-to-copper ratios fall in the absence of adequate taurine.[29] Deficiency of zinc or an elevated copper-to-zinc ratio (without adequate taurine) might therefore have a role to play in the genesis of seizures. Zinc might also reduce seizure activity by inhibiting aspartic acid neurotransmission.[15]

Dosage: The therapeutic dose of elemental zinc is probably in the range of 10-80 mg/day. Consideration should be given for simultaneous copper supplementation (i.e., 1-2 mg/day) if high doses of zinc (i.e., at or above 80 mg/day) are prescribed for more than a couple of years due to potential haematological problems resulting from chronic high-dose zinc supplementation.

Case 2: Dilantin resistance

This case was reported in the book, *Healing Nutrients Within*.[14] I include it here because the favourable effects were the result of combining taurine, manganese, and zinc.

"At the Brain Bio Center, we gave taurine successfully to many patients with seizure disorders. A sixty-six-year-old man with a history of seizures recently came to us. He had been put on Dilantin, but it failed to control his seizures. We maintained his dose of Dilantin but supplemented it with optimal doses of taurine (4 g), manganese (100 mg) and zinc (60 mg). Six months later, he was still free of seizures and his dose of Dilanitin was reduced."

Chromium (for consideration in suspected hypoglycaemia-associated seizures)

Gaby has suggested that both hypoglycaemia and hyperinsulinaemia might be involved in the pathogenesis of epilepsy.[8] Chromium has the most documented evidence to support its use as a blood-glucose-stabilizing molecule. For many years, chromium was thought to be involved in the glucose-tolerance factor (GTF) molecule that presumably increases insulin sensitivity. The composition of GTF, as isolated from yeast, is made of chromic ion, nicotinic acid, and the amino acids glycine, glutamic acid, and cysteine.[30] However, GTF of any type has never been found in human tissues. More recently, a naturally-occurring oligopeptide low-molecular weight chromium-binding substance (LMWCr) has been proposed to be the biologically-active form of chromium.[31] This compound has been found in many different types of mammals, and is widely distributed in numerous tissues (e.g., liver, kidney, spleen, intestine, testicles, and brain). This oligopeptide is also comprised of the amino acids glycine, cysteine, glutamic acid, aspartic acid, and has a multinuclear chromic assembly in which the chromic centers are bridged by the anionic ligands, oxide and/or hydroxide.[31] This LMWCr compound is part of an insulin amplification system that regulates glucose homeostasis through a complex series of biochemical reactions occurring at the insulin receptor.[32,33]

In one double-blind crossover experimental design study, eight female patients were given 200 mcg of supplemental chro-

mium (chromic chloride) for three months.[34] Supplementation improved the hypoglycaemic symptoms and raised the minimum serum glucose values 2-4 hours following the glucose load. Other improvements included an increase in the insulin receptor number and the binding of insulin to red blood cells. The authors of this study linked the aetiology of hypoglycaemia to impaired chromium nutrition and/or metabolism. In another study, 20 patients with clinical symptoms of hypoglycaemia were given 125 mcg of a yeast chromium supplement for three months.[35] Prior to taking chromium, 19 of 20 subjects had a minimal glucose level in the tolerance curve above 2.2 mmol/L (40 mg/dL), which is the limit for glucose-induced hypoglycaemia. The patients were assessed by the use of a glucose tolerance test (one gram of glucose/kg of body weight) and by an interrogation scheme. After three months of supplementation, 11 of 15 patients (73%) had improvements in the negative part of the glucose tolerance curve (i.e., the part of the curve being below the fasting level). Subjectively, the patients reported improvements in hypoglycaemic symptoms of chilliness, trembling, emotional instability, and disorientation. Thus, chromium as part of the LMWCr should have the ability to improve glucose tolerance, increase insulin sensitivity, and reduce suspected seizures if associated with episodes of hypoglycaemia.

In terms of toxicity, Lamson and Plaza have summarized the chromium literature, and evaluated its mechanisms of action and exceptional safety profile. According to these investigators, "there is no demonstration of general chromium toxicity in animals at a dose that would extrapolate to humans as 1,050 mg daily."[36] One of these investigators used 3,000-4,000 mcg of chromium as nicotinate given twice daily to adult-onset diabetic patients for months to years resulting in tremendous reductions of glucose and lipid levels without any increases in blood urea nitrogen, liver enzymes, or other laboratory abnormalities. It is interesting to note that high supplemental microgram doses of chromium would never come even close to 1,050 mg per day.

Dosage: I recommend 200-600 mcg/day of chromium for the treatment of suspected hypoglycaemia-associated seizures.

Case 3: Possible hypoglycaemia-associated seizures

I can recall a case of a patient in his twenties with a diagnosis of epilepsy who presented to the Robert Schad Naturopathic Clinic (Toronto, Ontario). He had two previous episodes of seizures. His neurologist was unable to determine the exact type and was considering complex partial seizures as the patient's diagnosis. During the seizures he experienced a partial loss of consciousness where he would lose sensations in his arms and feel paralysed, and some motor movements may have accompanied these episodes as well. He refused treatment with anticonvulsant medications and wanted to see if orthomolecular care would benefit his condition. His history revealed nighttime and early morning hunger, irritability when missing meals, and excessive cravings for sugar. We instituted dietary changes and gave him 400 mcg/day of supplemental chromium. We followed-up with this patient for approximately eight months after instituting treatment, and he no longer had any seizure episodes and felt well enough to resume his engineering studies.

Case 4: Generalized seizures possibly secondary to hypoglycaemia

This patient presented in 2008 with a probable diagnosis of generalized seizures when she came to my clinical practice (Toronto, Ontario). Her seizures were preceded by episodes of buzzing in the left ear followed by numbness ascending from the left foot to the left knee. Her initial EEG (April 2008) showed a potentially epileptiform disturbance over the right mid and posterior temporal region and to a lesser extent a similar independent finding over the left mid temporal region. Her MRI (May 2008) showed no space occupying lesion or focal abnormality of the temporal lobe. A subsequent sleep-deprived EEG was within nor-

mal limits and showed no epileptic activity.

At the first visit (November 2008), the patient informed me that she had five prior seizure episodes since they first began in March 2008. I diagnosed the patient with likely generalized seizures possibly secondary to hypoglycaemia. She was taking no anticonvulsant medication and also had her driver's license suspended as a result of the seizures. I prescribed the patient taurine (2,000 mg upon waking each day) and chromium (400 mcg at bedtime daily).

At the next appointment (December 2008) the patient reported one seizure since the initial appointment that was preceded by the typical buzzing sensations. I increased the taurine to 3,000 mg upon waking and the chromium to 600 mcg at bedtime. I also prescribed 1,500 mg of crystalline GABA to be taken at 10:30 pm each day.

At another follow-up (January 2009) the patient reported no seizures since the December appointment. No other treatments were prescribed.

In another follow-up (April 2009) appointment the patient reported no seizures since the December appointment even though she had four episodes of buzzing for the past four months without any evolution to seizure activity, however. I told her that she had to go for one full year of no seizure activity for her driver's licence to get reinstated. We were cautiously optimistic.

In May 2009, I received an email from the patient informing me that she had unfortunately experienced a seizure the Sunday evening. When she awoke, her bed was covered in urine and she had bitten her tongue. She was really upset since she went approximately five months with no seizure activity despite some buzzing.

We had our final visit (July 2009) and we agreed that she had to pursue anticonvulsant medication since the orthomolecular approach was unable to keep her seizure-free for 12 months. Since the patient reported possible seizure activity prior to her period, I instructed her to take 250 mg of vitamin B_6 and 150 mg of magnesium daily until our September or October follow-up. This was the last appointment I had with this patient. I assume she pursued anticonvulsant medication and exclusively worked with a neurologist.

Vitamin B_3

In Hoffer's review of the literature, both niacin and niacinamide were shown to have some sedative activity, and were able to potentiate the action of sedatives, anticonvulsant medications and certain tranquilizers. I recommend using niacinamide instead of niacin since this type of vitamin B_3 is seldom associated with cutaneous flushing. Niacinamide possess benzodiazepine-like effects,[38,39] which stimulate the GABA system and theoretically would reduce seizure activity. Benzodiazepines are used to manage seizures based on physiologic effects that are mediated through the GABA receptor.[40] It seems reasonable, therefore, to prescribe therapeutic doses of niacinamide to perhaps increase the anti-seizure efficacy of benzodiazepines and other anticonvulsant medications.

Dosage: The therapeutic dose needs to be adjusted according to each patient's clinical response. Start with 500 mg/day of niacinamide and slowly increase the dose until its efficacy can be determined. I would not increase the daily dose of niacinamide beyond 2,500 mg since larger doses can be associated with nausea and even vomiting.

Additional Orthomolecular Considerations

Gaby recommends that other nutritional supplements (e.g., vitamin E, biotin, folic acid, thiamine, and essential fatty acids) and specific diet modifications be considered as treatments for seizures.[8] He reviewed food allergy, the ketogenic diet, and even the Atkins diet as potential therapies. The reader is encouraged to review Gaby's article prior to instituting any of these additional treatments.

Clinical Management of Epilepsy

1. Let your patients know that the orthomolecular approach is probably not adequate to fully replace anticonvulsant medications.

2. The goals of instituting orthomolecu-

lar treatments are to increase overall quality of life, reduce the frequency of seizures, and to possibly reduce the amount of required medications. The orthomolecular approach is not meant to cure seizures.

3. Paediatric patients do not like taking pills of any kind, especially when they taste bad. When treating paediatric patients, work with the parents and think of creative ways to ensure compliance.

4. Hypoglycaemia is an overlooked possible cause of seizures. I believe that hypoglycaemia occurs more frequently in the adult cases. With the supplemental use of chromium and some dietary modifications, it should be possible to determine in a few months if the orthomolecular treatments are helping, and if hypoglycaemia was partly responsible for seizure activity.

5. Don't be discouraged if none of the orthomolecular treatments work. Some seizure cases can be very difficult to treat so educate your patients about realistic outcomes from the adjunctive use of orthomolecular medicine.

Conclusion

Epilepsy can be difficult to treat since some patients might be resistant to their anticonvulsant medications. At the very least, the orthomolecular approach probably provides some benefit in reducing the frequency and intensity of seizure activity. Given how safe and cost-effective the orthomolecular approach is, the use of the orthomolecules described above should be considered when patients (after having made an informed decision) want to complement their anticonvulsant medication, seek an alternative to anticonvulsant medication, or have not responded adequately to their anticonvulsant medications. More clinical studies are certainly needed, especially augmentation trials in which orthomolecules are taken alongside anticonvulsant medication. Until such trials happen, clinicians should feel comfortable recommending these specific orthomolecules to their patients based on evidence of anti-seizure activity.

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Competing Interests

The author declares that he has no competing interests.

Statement of Informed Consent

Written consent was obtained for cases one and four. Case Two was published in a book and the reference has been provided. Case Three was lost to follow-up and it has been impossible to find this patient.

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Journal of Orthomolecular Medicine,
16 Florence Avennue, Toronto,ON,Canada M2N1E9
editor@orthomed.org

All manuscripts will be subjected to a peer review process once they have been approved by the Editor.

Editorials

Editorial style articles (limited to 2,500 words) will be considered. An abstract is not required. Editorials will normally be requested by the editor; however, we will consider unsolicited manuscripts.

Clinician's Letters

Letter from clinicians (limited to 2,000 words) can be requested by the editor or suggested from potential authors with at least ten years of clinical experience as a practicing orthomolecular practitioner. We welcome suggestions from elder orthomolecular practitioners on particular clinical pearls.

Short Communications

We encourage short communications (limited to 1,000 words) in the form of letters to the editor that stimulate debate and provide relevant commentary, especially on articles published in the journal.

Original Research

Original research manuscripts will be considered. Such articles are papers that report clinically relevant investigations or observations within the journal's scope of interests. The abstract should be structured (as described in page two of "Instructions to Authors"), the text should not exceed 5,000 words, and there should be approximately 20 to 40 references. Figures and tables are encouraged and should be included where possible; however, data should not be repeated in both a table and a figure and accompanying text need not reiterate the information provided in tables and figures.

Brief Reports

Brief Reports are condensed articles with a focused message. They should include a brief abstract of no more than 200 words, text of no more than 1,500 words, 5-15 references, and two tables or figures.

Case Reports/Series

Case reports provide a summary of a single case or several cases and give a concise review of the literature. Case reports should present unusual aspects of common problems or novel perspectives upon, or solutions to, clinically relevant issues. They should include a brief abstract of no more than 200 words, text of no more than 3,000 words, and there should be approximately 10-30 references. For further advice on writing detailed case reports, please refer to Aronson JK: Anecdotes as evidence. BMJ, 2003;326:1346.

Synthesis Papers

We welcome articles of an academic nature that are educational to the orthomolecular community. We also welcome articles that may be hypothesis generating and may create dialogue within the readership. They should include a brief abstract of no more than 200 words, text of no more than 3,000 words, and there should be approximately 10-30 references.

Review Articles

Review papers provide a synthesis of topics related to clinical aspects of orthomolecular medicine. The text should not exceed 5,000 words and have an abstract that does not exceed 200 words. Review papers can be written as focused systematic reviews or more broadly as narrative reviews.

Viewpoints/Opinion Pieces

Viewpoints are somewhat review in nature; however, they are designed to provide an argument to convince the reader. The text should not exceed 2,000 words and have an abstract that does not exceed 200 words. This type of narrative paper presents the opinions of an author or authors rather than providing a balanced literature review or new experimental data.

Educational Articles

Educational articles are written for a broad audience in order to provide specific instructions on how a specific research methodology can be used or how to best employ a therapy. They should include a brief abstract of no more than 200 words, and text of no more than 3,000 words.

Reprints

Authors may order reprints, at regular rates, by completing order forms sent with their published article.

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Instructions to Authors

Submission Requirements

The requirements for publishing in the Journal of Orthomolecular Medicine are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals." http://www.icmje.org. Email is the preferred method of submission and should be sent to the following email address: editor@orthomed.org. If this is not possible, submit manuscript in duplicate, double-spaced on standard paper. Author's full names, academic or professional affiliations and degrees should be given. A CD or flash drive containing the text of the paper must be included, specifying the file name and program used.

Electronic Submissions should Include the following

1. A copy of the text with tables and references 2. Individual files for each figure 3. Indicate in your cover letter at least three individuals who could act as peer reviewers for your manuscript.
Please provide the names, institutional affiliations, and email addresses for each of these individuals. 4. Electronic submissions should use a standard, current word processing system. 5. Label the attached files by primary author's last name, short title of the article, and date submitted.

References

In the manuscript, reference sentences are ended with a reference number.[3] Journals cited should conform to standard abbreviations (ie. American Journal of Clinical Nutrition is cited as Am J Clin Nutr). Book references are not abbreviated. Manuscript references should be listed consecutively, in the order in which they are cited, as follows. Abbreviate four or more authors to et al after the third author.

For Journal References Cited

1. Pauling L, Itano HA, Singer SJ, et al: Sickle cell anemia: a molecular disease. Science, 1949; 110: 543–548.
For books cited: 2. Williams RJ: Biochemical individuality. New York. John Wiley & Sons. 1973; 32–36.
For papers cited from books: 3. Cameron, E: Vitamin C, Carnitine and cancer. In. eds. Bland J. A year in nutritional medicine. New Canaan, CT, Keats Publ. 1986; 115-123.

Tables and Illustrations

Placement in manuscripts should be indicated with a line break and the entry: Place Table/Illustration 1 here. Include illustrations, tables and photographs on separate sheets, identifying each with number referring to manuscript placement. Illustrations and diagrams on CD must be created using a vector based drawing program and saved in EPS or 300 dpi TIFF file format. Create tables using column tabs rather than spaces. Legends must accompany each illustration. The author will assume the cost if illustrations require re-rendering.

Abstracts

For original research provide an abstract of 500 words or less, which must include the following subheadings: Background, Objectives, Design, Setting, Intervention, Main Outcome Measures, Results, Conclusions, and Trial Registration. All other types of papers require abstracts of 200 words or less, and should not follow the abstract format described here for original research papers.

Competing Interests Statement

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors should disclose any financial competing interests but also any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript. Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read "The author(s) declare that they have no competing interests."

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Author's Corrections

Proofs will be submitted to authors for correction; prompt return will facilitate prompt publication.

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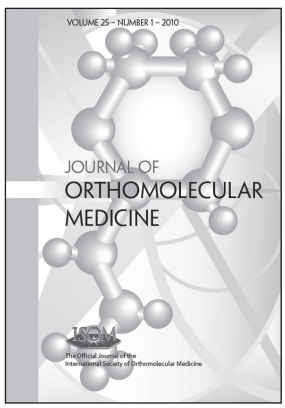

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