

The Clinical use of Orthomolecules in the Treatment of Schizophrenia: Critical Reflections and Commentary

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Abstract *The syndrome of schizophrenia is marked by changes in the afflicted person's functioning, perception, thinking, and behaviour. The mainstay of treatment involves antipsychotic medications (either the older generation, and /or more commonly, the newer atypical antipsychotic medications), often combined with other psychiatric medications (e.g., anxiolytics, hypnotics, mood stabilizers, and/or antidepressants), as well as some psychoeducation. The "typical" schizophrenic patient seeking out the author's care has either been ill for a brief time (perhaps a year or less) or many years, has relapsed once or several times following the abrupt discontinuation of medication, has developed physical problems from medication (e.g., weight gain and tardive dyskinesia), and has accumulated a host of disabling behavioural and emotional coping strategies. Specific orthomolecular substances can reduce symptoms of psychosis, attenuate weight gain, and help to reduce symptoms of tardive dyskinesia and even neuroleptic-induced akathisia. Unfortunately, the long-term use of antipsychotic and other psychiatric drugs given to assuage symptoms of schizophrenia often cause devastating impacts on the bodies and brains of the individuals that take them. This makes it difficult, if not impossible for the orthomolecular approach to help patients fully recover.*

Introduction

The syndrome of schizophrenia is marked by changes in the afflicted person's functioning, perception, thinking, and behaviour. The onset can be sudden or take many years to reach some critical threshold, at which point the "illness" becomes so observable that it forces some type of action or intervention. Most individuals experience a prodromal phase in which there is gradual deterioration (e.g., social withdrawal, loss of interest in school or work, poor attention to personal hygiene, strange behaviour, and episodic outbursts of anger) eventually forcing families to recognize that something is wrong, although they might not be able to

fully recognize how serious the situation is.¹ If afflicted individuals manifest overt symptoms of psychosis (i.e., some combination of delusions, hallucinations, disorganized speech and/or behaviours, and/or flattened affect or avolition), that normally results in a clinical diagnosis of schizophrenia particularly after other possible causes have been ruled-out.¹

Schizophrenia has a prevalence of one percent. It characteristically affects males in their late teens or early twenties, and females in their late twenties or early thirties.¹ It is considered a polygenetic disorder. Environmental and developmental factors can influence an individual's vulnerability to being

diagnosed with schizophrenia.² Biomedical research has had a difficult time figuring out “how a genetically mediated, neurodevelopmental disorder is not expressed clinically until 1.5–3 decades postnatally, but then proceeds to progressively disable its victims.”²

The mainstay of treatment involves antipsychotic medications (either the older generation, and/or more commonly, the newer atypical antipsychotic medications), often with combinations of other psychiatric medications (e.g., anxiolytics, hypnotics, mood stabilizers, and/or antidepressants), as well as some psychoeducation. While some afflicted individuals experience symptom reductions (and possibly remissions) when treated early in the course of their illness, the majority go on and off their psychiatric medications. This is believed to explain frequent relapses and remissions following treatment.² Unfortunately, this is associated with clinical deterioration and declining functionality over time.²

This difficult reality becomes a serious problem for clinicians trying to manage these individuals. Patients are often loaded-up on several psychiatric medications, which they have been told will be needed for the rest of their lives as a result of the expected chronicity of the syndrome. Many of these individuals detest how medications make them feel and frequently discontinue their pills abruptly with hopes of not needing them any longer. This typically results in destabilization and relapse, often requiring hospitalization and being re-prescribed several psychiatric medications. More plausibly, however, destabilizations can result from a) abruptly discontinuing or quickly tapering a biologically-habituated antipsychotic medication (as well as other medications), and/or b) neuroplastic changes arising from the frequent use of antipsychotic medication (i.e., drug-generated buildup of supersensitive dopamine receptors). Arguably those factors are more responsible for the chronicity of schizophrenia than medication non-compliance.^{3,4}

Many sick individuals are pushed into assuming the role of the “mentally-ill” pa-

tient. They are often coerced into becoming lifetime consumers of powerful antipsychotic medications and other biomedical treatments. My clinical experience has shown that almost all such diagnosed individuals are held at bay and diminished by the very antipsychotic medications given as solutions to their psychotic symptoms. Antipsychotic medications work by suppressing or disabling the nervous system, which makes these individuals indifferent and apathetic.⁵ These medications seem to undermine intrinsic motivational systems, reduce vitality, cloud and disable vulnerable brains, and make progressive and life-affirming changes extremely difficult to accomplish. I believe they also lead to behavioural disinhibition, and even a regression of emotional maturity.

I have seen too many individuals on these medications become self-absorbed, and focus on activities that involve immediate gratification (e.g., internet pornography, substance use/abuse, pathological gambling, and/or food-based addictions). They are rendered less capable of engaging in age-appropriate types of employment or volunteer activities. I don't believe that my observations are spurious since it is known that antipsychotic medications up-regulate the dopamine-type II receptors, which in turn reduces the functioning of dopamine-type I receptors. These changes have been linked to the presence of negative symptoms (i.e., defined as avolition, apathy, flat affect, and reduced social engagement).⁶ Some highly questionable research demonstrates that schizophrenia is associated with hypofrontality,⁶ which means reduced activation to the frontal regions of the cerebral cortex. I am more convinced that the observed hypofrontality results from taking medications that diminish motivation and cognitive capacity by undermining the brain's executive functioning.

Thus, the “typical” schizophrenic patient seeking out my care has either been ill for a brief time (perhaps a year or less) or many years, has relapsed once or several times following the abrupt discontinuation of medication, has developed physical problems from medication (e.g., weight gain and

tardive dyskinesia), and has accumulated a host of disabling behavioural and emotional coping strategies. Given this reality, how can I begin to mitigate symptoms and enhance patients' quality of life, while also helping to overcome the numerous negative effects that continue to accrue from the very psychiatric medications given to "stabilize" these individuals? This medical conundrum often overwhelms my clinical capabilities. Too few clinicians wish to honestly and openly address this obvious "elephant in the room."

I can offer hope, education and lifestyle counselling, and I can recommend evidence-informed orthomolecules* that may confer some symptom-reducing effect and/or perhaps lessen some of the negative impacts of antipsychotic medications. In this article, I will review some of best studied and easily obtainable orthomolecules for schizophrenia and comment on their clinical effectiveness. I will keep the discussions about biochemical mechanisms to a minimum since it is difficult to know precisely how particular orthomolecules work. Over decades, orthomolecular researchers and clinicians have noticed that certain orthomolecules have favourable effects. I will also attempt to show the different types of outcomes that can be expected when complementing psychiatric medications with orthomolecular substances.

Evidenced-Based Orthomolecules

While there are literally hundreds of studies on numerous orthomolecules for many health-related issues, only limited studies, some done decades ago, have evaluated the clinical merits of orthomolecules to address symptoms of schizophrenia. Without current robust research to support the clinical use of orthomolecules for schizophrenia, clinicians have to create reasonable plans for their schizophrenic patients based on clinical experience and not from numerous well-conducted clinical trials involving scores of patients.

*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.

Glycine

One of more evidenced-based orthomolecules is glycine, an amino acid that functions as an inhibitory neurotransmitter in the central nervous system (CNS).⁷ With respect to schizophrenia, the pathophysiology of the disorder is believed to involve hypofunction of glutamatergic N-methyl-D-aspartate receptors (NMDAR).^{8,9} Glycine functions as a full agonist of the glycine site of the NMDAR, and has been shown to reduce negative symptoms of the disorder.⁸ Based on my review of the pilot clinical trials done with this orthomolecule, the dose range is 0.8 g/kg per day.¹⁰⁻¹⁴ It possibly benefits patients that are maintained on the older type or first-generation antipsychotic medication. Glycine might be contraindicated, however, when combined with the second-generation or atypical antipsychotic medication. One clinical trial showed a slight worsening of psychotic symptoms (as shown by an increase in the Brief Psychiatric Rating Scale scores) when glycine was combined with clozapine.¹³ A similar clinical trial showed no added benefit (and no clinical worsening) when glycine was combined with clozapine.¹⁴

The use of glycine should be considered, even though it might only have potential value when prescribed to patients maintained on first-generation antipsychotic medication. In my opinion, antipsychotic medications are mostly responsible for the observed negative symptoms.⁶ Glycine ought to be tried since it might reduce some of the medications' affect-suppressing and nervous system disabling properties. I have not observed any negative reactions from therapeutic doses of glycine, except that some patients do not like the taste even when mixed in diluted fruit juice. It needs to be taken away from meals and it requires good compliance.

N-Acetylcysteine (NAC)

NAC is a precursor to glutathione, which is presumed to be deficient in the brains of schizophrenic patients.¹⁵ NAC has been shown to increase plasma glutathione levels.¹⁶ NAC also supplies cysteine, serving as substrate for the glutamatergic

system; thus, NAC influences or modulates the glutamatergic system in a manner that might also reduce symptoms.¹⁷ A clinical trial evaluated the safety and effectiveness of NAC (1,000 mg twice daily over 24 weeks) as augmentation to medicated patients with chronic schizophrenia.¹⁸ Compared to placebo, the patients treated with NAC had improvements in their negative symptoms, global function, and akathisia. The improvements ceased within one month of discontinuing the orthomolecule. These improvements are noteworthy since all these patients were ill for an average of 12 years, and more than 60% were taking clozapine. A similar study showed statistically-significant improvements in negative symptoms among chronic schizophrenic patients given NAC (up to 2,000 mg per day) in combination with risperidone (taking up to 6 milligrams per day).¹⁹ Thus, the benefits of NAC are similar to glycine, except that it can be safely combined with atypical antipsychotic medication and might also benefit akathisia. The only limiting factor is that some patients experience very unpleasant nausea or stomach upset, which can be intense so this orthomolecule should be taken away from food.

L-Lysine

By inhibiting L-arginine transport, the supplemental use of L-lysine is believed to decrease nitric oxide levels, which can favourably impact symptoms of schizophrenia (i.e., the "nitric oxide dysregulation hypothesis of schizophrenia").²⁰ In a single-blinded, randomized, crossover pilot study, L-lysine (6,000 mg daily) or placebo was given for four weeks to 10 patients with schizophrenia as an adjunct to their antipsychotic medication, and then treatment was crossed-over for another four weeks.²⁰ The use of L-lysine was associated with statistically-significant increases in L-lysine blood concentrations (eight out of 10 patients; $p < 0.05$), and statistically-significant decreases in the positive symptoms of the disorder ($p < 0.001$). The use of L-lysine did not perturb levels of the other amino acids tested, i.e., citrulline, arginine, proline, glutamate and alanine.

However, based on further data analysis, the reductions in positive symptoms could not be solely attributed to that of the L-lysine supplementation. In addition, three patients self-reported improvements. Two patients noted decreases in their positive symptoms (i.e., auditory hallucinations) but those returned following trial termination. One patient reported improved attention while taking L-lysine, while another noted improved mental stability and memory capacity that continued for several weeks after the trial ended.

While these results are preliminary, they suggest that L-lysine augmentation might reduce positive symptoms of schizophrenia and perhaps confer some cognitive benefits as well. No significant adverse side effects were associated with L-lysine treatment, except transient gastrointestinal problems. The use of L-lysine was not associated with any extrapyramidal effects. The remarkable finding from this small pilot trial is that all the patients given L-lysine had been ill for a duration of 3-29 years, and were on various combinations of atypical antipsychotic medications (6 of 10 patients were taking at least two atypical antipsychotic medications).

It does appear that L-lysine can be combined with any type of atypical antipsychotic medication as a safe augmentation strategy, and could be given with the older types of antipsychotic medications as well.

L-Theanine

This amino acid apparently increases both dopamine and serotonin, although a study in rats showed that it might decrease serotonin.²¹ It also increases alpha brain-wave activity, which facilitates relaxation without causing sedation.²¹ In a randomized, double-blind, placebo-controlled trial, L-theanine or placebo was given to schizophrenic and schizoaffective disorder patients as an augmentation to antipsychotic medication.²² Sixty patients were randomized to placebo or L-theanine (400 mg daily) for eight weeks, but only 40 patients completed the trial. Compared to placebo, L-theanine was associated with statistically significant reductions

in the following: anxiety ($p=0.015$), positive symptoms ($p=0.009$), and general psychopathology scores ($p<0.001$). According to the 5-dimension model of psychopathology, the use of L-theanine was also associated with statistically significant reductions over placebo in positive symptoms per the Positive and Negative Syndrome Scale ($p=0.004$), and activation factor ($p=0.006$).

Another study evaluated serum levels of various neurochemicals from the same 40 patients that completed the previous trial.²³ Analysis of the serum levels showed the beneficial effects of L-theanine to be associated with circulating levels of brain-derived neurotrophic factor and the cortisol-to-dehydroepiandrosterone ratio.

I have not observed any negative effects from the use of L-theanine and believe it would be safe to combine it with all classes of antipsychotic medication.

B-Complex Vitamins

Problems in one-carbon metabolism have been associated with schizophrenia, even though it is difficult to determine why this occurs.²⁴ Not all studies have shown patients with schizophrenia to have high plasma homocysteine levels or even methylene tetrahydrofolate reductase (MTHFR) polymorphisms. Those sorts of findings could explain problems with one-carbon metabolism. It is interesting to note that high plasma homocysteine levels have been associated with neurotoxicity through its effect on NMDARs. As discussed earlier, one biochemical theory of schizophrenia implicates NMDAR hypo-function as being etiologic.

In a randomized controlled trial, 42 schizophrenic patients with plasma homocysteine levels greater than 15 $\mu\text{mol/L}$ were randomized to daily vitamin treatment (2 mg of folic acid, 25 mg of vitamin B₆, and 400 mcg of vitamin B₁₂) or placebo.²⁵ The vitamin and placebo groups were treated for three months, and then the groups were crossed-over for another three months (i.e., the group that had initially received vitamin treatment was put on placebo, and the group initially on placebo received vitamin

treatment). Compared to placebo, the results revealed significant declines in homocysteine levels and statistically significant improvements in the positive and negative symptoms of schizophrenia (as measured by the Positive and Negative Syndrome Scale). In addition, neuropsychological test results were also improved (especially, the Wisconsin Card Sort Test, a measure of executive function) in the vitamin group compared to placebo. The authors were not sure why high homocysteine levels occur among some schizophrenic patients, but they did relate the high levels to low folate or vitamin B₁₂ deficiency, polymorphism of MTHFR, obesity, smoking, or excessive caffeine consumption. The authors concluded that a subgroup of schizophrenic patients with high plasma homocysteine levels might benefit from the use of these B-vitamins, but they also noted that a high level of homocysteine might not be a prerequisite to benefiting from the vitamin treatment.

These results are promising since therapeutic effects were noted from very low daily doses of orthomolecules. Additionally, these small amounts were able to confer benefits upon the executive functioning, which is usually impaired among patients with schizophrenia. I recommend that a good B-complex 50 or 100 is taken at least once daily and with additional folic acid so that the daily amount is at least 2 mg. B-complex vitamins will not interfere with any of the classes of antipsychotic medication, and are generally well tolerated as long as the vitamins are ingested with food. If taken on an empty stomach, the nausea and stomach discomfort can be substantial. B-complex vitamins will also cause yellowing of the urine, which is not a concern but patients need to be told about this so they don't become unduly worried.

Omega-3 Essential Fatty Acids

The therapeutic use of omega-3 essential fatty acids would probably help some of the cardiometabolic problems that are associated with antipsychotic medications, particularly the atypical ones. However, when looking at

the therapeutic value of omega-3 essential fatty acids, the research is not abundantly unanimous or even clear on the expected benefits with respect to symptom moderation. In the National Institute for Care and Health Excellence (NICE), the evidence is inconclusive, with four randomized controlled trials showing no benefit and another four randomized controlled trials showing benefit.²⁶ In the trials that showed benefit, patients with schizophrenia did have statistically significant reductions in positive and negative symptoms, but these improvements were likely minimal from a clinical perspective. In addition, the numbers of patients were low. Low patient numbers in a pilot trial can over-estimate the clinical benefits (i.e., a Type I error).

I continue to prescribe omega-3 essential fatty acids, but recognize that their clinical impacts are not large. Patients can experience mild gastrointestinal symptoms, such as diarrhoea, dyspepsia, or nausea.²⁶ The dose of eicosapentaenoic acid should be at least 2 g daily. It can be safely combined with all classes of antipsychotic medications.

Vitamin C (Ascorbic Acid)

The argument has been put forth that all humans suffer from an inherited condition known as hypoascorbemia, which means that a steady supply of vitamin C is needed from the environment (i.e., from food and/or supplements) to overcome our biochemical and physiological dependency on this vitamin.²⁷ In a study evaluating chronic schizophrenic patients, the plasma and urinary vitamin C levels of 35 schizophrenic patients were compared to an equal number of controls.²⁸ All subjects were given the same hospital diet and 70 mg of vitamin C daily for four weeks. Baseline plasma vitamin C values were lower in the schizophrenic patients ($p < 0.05$), but normalized to approximately the same as the control group after the four weeks of treatment. The mean vitamin C levels as measured in a six hour urine collection were different among the low excretors of both groups, and this reached statistical significance ($p < 0.05$) –

15.9 mg for schizophrenics and 39.5 mg for the controls.

When all the schizophrenic and control subjects were given a loading test of 1 g of vitamin C after the four weeks of 70 mg of vitamin C daily, the schizophrenic patients continued to excrete lower amounts of vitamin C in their urine compared to the control values. After the loading test, the plasma levels of vitamin C were different with the schizophrenic patients having a lower mean value than the controls ($p < 0.05$). After one month of supplementation with 1 g of vitamin C, the plasma levels of each group equalized, as did the six hour urinary excretion rates. The authors of this study were in agreement with the hypothesis that “schizophrenic patients require higher levels of vitamin C than the suggested optimal ascorbic acid requirement for healthy humans.”

A report by Smythies described some of the therapeutic functions that vitamin C has upon the brain including its ability to protect NMDARs from glutamate toxicity, antagonize the effects of amphetamines, enhance the therapeutic efficacy of the older class of antipsychotic medication (e.g., haloperidol), and prevent the auto-oxidation of dopamine to its toxic derivatives.²⁹ It is therefore biologically and clinically plausible that patients with schizophrenia require doses of vitamin C to optimize their metabolic needs. A randomized controlled trial combined 500 mg daily of vitamin C to atypical antipsychotic treatment for 8 weeks.³⁰ The results demonstrated that that addition of vitamin C improved antioxidant status and resulted in statistically significant reductions in symptoms as per decreases in the Brief Psychiatric Rating Scale.

Vitamin C can be safely combined with all of the usual treatments for schizophrenia. Since vitamin C has a short half-life, Hoffer suggested divided daily doses of up to 3,000 mg,²⁷ but starting doses can be between 500–1,000 mg. On the higher daily doses, some patients might experience gas, bloating, loose stools, and/or diarrhea until the dose is lessened.

Vitamin B₃

Hoffer and other researchers discovered a relationship between vitamin B₃ (i.e., niacin/nicotinic acid or niacinamide/nicotinamide), pellagra and schizophrenia. It is known that a subset of patients with schizophrenia will have a reduced skin flush response to topical methylnicotinate,^{31,32} and reduced skin sensitivity has been associated with greater functional impairment among patients with schizophrenia.³³ Research by Miller et al has shown an *in vivo* impairment in the ability to synthesize dietary tryptophan to nicotinamide adenine dinucleotide because of an up-regulation of the kynurenine pathway in some deceased patients with schizophrenia.³⁴ The authors reported that these results might be due to a diminished niacin effect; possibly, the result of depressed production or reduced signal transduction via the niacin receptor. They noted that niacin or its congeners are obligatory regulators of this biochemical pathway and should be capable of restoring homeostasis. In follow-up research by Miller and Dulay, evaluations of post-mortem brain tissues of schizophrenic patients showed that the protein for the high-affinity niacin receptor was down-regulated in the anterior cingulate cortex.³⁵ This suggests that the peripheral defects reported above also extend to the brain.

It should be noted that the number of post-mortem brains evaluated was very small, which makes it very difficult to generalize these unique findings to a broader group of patients with schizophrenia. While this research excluded smoking and antipsychotic medication as possible causes,^{30,31} it is unclear whether these findings reflect some unique biochemical abnormality specific to patients with schizophrenia. It seems more plausible that lifestyle, the impacts of substance use and/or abuse, the neuroplastic changes resulting from antipsychotic and other psychiatric medications, as well as other unknown (but explainable) factors are more responsible for these findings. Even so, these findings suggest an increased need for vitamin B₃ among patients with schizophrenia.

I continue to use vitamin B₃ even though

modern randomized studies are summarily lacking. When Hoffer reported his excellent outcomes from several randomized controlled trials decades ago, vitamin B₃ was given to patients very early in the course of their psychoses along with usual care (i.e., some combination of psychiatric medications and sometimes electroconvulsive therapy) and compared to usual care by itself.^{36,37} It is a challenge to apply these clinical trial results to the mental health care of today's patients since the current psychiatric care provided to patients with schizophrenia is vastly different from the 1950s and 1960s. Even Hoffer reported that vitamin B₃ cannot overcome the "tranquilizer psychosis," a term he used to describe the harmful and often devastating effects that atypical antipsychotic medications have upon the bodies and brains of individuals taking such medications.³⁸ Hoffer observed clinically that no amount of vitamin B₃ could reverse the tranquilizer psychosis that patients experienced from atypical antipsychotic medications, and thus patients were not likely to recover unless they were tapered down or weaned off of psychiatric medications (after stabilizing).

Hoffer also reported on the efficacy of vitamin B₃ when administered to patients with chronic schizophrenia. Chronic patients required vitamin B₃ treatment for five or more years in order to derive observable benefits.^{39,40} In one study involving 32 chronic patients, all the patients failed to respond to vitamin B₃ after two years of use. Nineteen of the patients discontinued the vitamin, and the remaining 13 patients continued with the vitamin treatment. Data was obtained for the years, 1956-1957, 1958-1959, 1960-1961, 1962-1963, and 1964.³⁹ Of the patients not on niacin, the mean number of days spent in hospital were 691 compared to 79 in the niacin group. Also, the proportion of time spent in the hospital was substantially less for the chronic patients who remained on the vitamin. In another analysis of 27 chronic patients who had been under treatment for at least 10 years, consistent treatment with vitamin B₃ produced the following results: 11 patients were able to work; two patients were able to marry and

look after their family and home; two patients were single mothers able to take care of their children; and three patients were able to manage their own businesses.⁴⁰ These results are striking when one considers the state of these patients prior to receiving orthomolecular care. The average age of these patients was 40, the majority of them were ill for seven years before they sought treatment from Hoffer, and all had been unresponsive to previous treatments. It should be noted, however, that when Hoffer treated these chronic patients with success they were not on atypical antipsychotic medication, which as mentioned above, undermines any potential efficacy that niacin possesses. Unfortunately, there have been no recent randomized controlled trials evaluating the efficacy of vitamin B₃ for early schizophrenia or first-episode psychosis, or for patients with chronic schizophrenia.

I am not sure if Hoffer's recommended dose ranges can help, given the current reality of patients loaded-up on psychiatric medications. It is doubtful that vitamin B₃ in any amount will overcome the negative psychoactive effects that these medications induce. I have not observed too many successes with optimal doses of the vitamin (3,000 mg or more daily) among chronic patients also taking prescribed cocktails of psychiatric medication that typically include at least one or more of the atypical antipsychotics. In my opinion, the capacity of vitamin B₃ to mitigate symptoms of psychosis has diminished significantly as a result of how patients with schizophrenia are managed by today's physicians.

What can reasonably be expected from vitamin B₃ treatment? My clinical experience has shown some ability of vitamin B₃ to help with the worrisome cardiometabolic effects of antipsychotic drugs, improve cognitive function, and somewhat lessen the intensity of psychotic symptoms, but these therapeutic effects are usually temporary. Normally something happens to necessitate a change in antipsychotic medication, which tends to result in further complications and less therapeutic responsiveness from vitamin B₃ or any other orthomolecular treatment.

Orthomolecules for Tardive Dyskinesia, Akathisia, and Weight Gain

Tardive dyskinesia (TD) is a devastating involuntary movement disorder that can result from treatment with antipsychotic medication. Sadly, this may not be reversible even when medication is discontinued. TD affects the orofacial area, but all parts of the body can be affected manifesting as myoclonic jerks, tics, chorea, and dystonia. These symptoms increase when patients are stressed or aroused, lessen when patients are relaxed, and remit during sleep.⁴¹ TD is associated with an increase in mortality ($p < 0.001$), but this statistic can become non-significant if one factors in age and the type of antipsychotic used.⁴² Patients on older (i.e., first generation) antipsychotics were twice as likely to die compared to those on atypical antipsychotics ($p < 0.02$), and for patients between 53 and 65 years of age, the use of older antipsychotics was linked to a sevenfold increase in mortality.⁴²

Several orthomolecular treatment options have been studied and found capable of reducing symptoms of TD. Vitamin E (D-alpha tocopherol) has been shown to reduce symptoms of TD⁴³ likely through its antioxidant effects and by increasing superoxide dismutase levels.⁴⁴ Not all studies with vitamin E have shown benefit.⁴⁵ In a randomized clinical trial, the use of 10 mg of controlled-release melatonin was found helpful in reducing symptoms of TD over a duration of six weeks.⁴⁶ In another trial, 20 mg of immediate-release melatonin was significantly helpful in treating TD among only two patients given the hormone. The remaining patients did not benefit from it.⁴⁷ Since two patients from this study had a marked benefit from melatonin, it might benefit a subgroup of patients who have this negative outcome from antipsychotic medication. Melatonin helps by attenuating the dopaminergic activity in the striatum and the release of dopamine from the hypothalamus; which suggests why it might help in the treatment and prevention of TD. Vitamin B₆ can also reduce symptoms of TD^{48,49} and even acute neuroleptic-induced akathisia.^{50,51} The mechanism of action for vitamin B₆'s effect upon TD and

akathisia is unclear, but it may influence the dopaminergic system and counteract some of the negative effects that the medications have upon the motor system.

Clinicians should choose 1-2 options among all the orthomolecular treatments identified here and assess the benefit over a period of 2-3 months. If no beneficial results are observed, discontinue the orthomolecular treatment(s) and try 1-2 others for another 2-3 months. If no change in TD and/or akathisia results after several therapeutic trials, it would be prudent to refer the patient to a neurologist who focuses on movement related disorders due to antipsychotic medication. The suggested dosages for therapeutic trials include: Vitamin E (800 IU twice daily), vitamin B₆ (600 mg twice daily for only 5 days for acute neuroleptic-induced akathisia, and then 400 mg daily thereafter for TD), or melatonin (10-20 mg of a controlled-release preparation at bedtime).

With respect to weight gain, which can be tremendous from the atypical antipsychotic medications, only alpha-lipoic acid has shown the ability to attenuate some of the abnormal increases in body weight.^{52,53} Alpha-lipoic acid should be used in daily doses of 1,200 mg since this dose can arrest some of the significant weight gain associated with these medications.⁵³ I have not seen any patient experience negative effects from the daily use of alpha-lipoic acid.

Summary

When reviewing the potential therapeutic benefits from the above-mentioned orthomolecules, it appears that they can moderate psychotic symptoms and improve cognitive function. In **Table 1** (p.150) is a summary of this data.

Table 2 (p.150) lists the orthomolecules with some potential in reducing some of the devastating neurological and cardiometabolic effects from antipsychotic medication.

Discussion

When thinking critically about the effectiveness of the orthomolecular approach, as applied to patients with schizophrenia, the

outcomes are not going to be too substantive as long as patients are maintained on high doses of antipsychotic medication and other psychiatric medications. As noted earlier, patients become tranquilized as a result of their psychiatric medications, especially the atypical antipsychotic ones, which create enormous dependency states associated with numerous brain- and body-based harms and complications.⁵⁴ These effects undermine the benefits of orthomolecular substances, and cause massively repressive effects upon human potential and growth.⁵⁵

How are clinicians supposed to work within this paradigm of mental health care that aggressively promotes the long-term use of psychiatric medication? There are no straightforward solutions, and as stated earlier, I am often overwhelmed trying to assist patients ill with schizophrenia who appear to have been damaged by the very psychiatric medications intended to help them.

In my experience, as long as patients chronically remain on their potent mix of psychiatric medications, their outcomes are not good. Schizophrenia is not a degenerative brain disease, and some 20-54% of patients can fully recover.⁵⁶ The long-term use of antipsychotics leads to fewer recoveries⁵⁶ compared to being off these medications for many years.^{57,58} These results have little to do with personality factors or the premorbid mental states of patients, and much more to do with the very psychiatric medications promoted as “essential” components to their full recovery. As is known, “these patients are typically forced to take heavy tranquilizing drugs or even undergo electroconvulsive shock therapy, severely impairing their most important resources—hope, meaning, and connection with their aliveness.”⁵⁶ Full recoveries while taking orthomolecular substances or even benefiting from well-intentioned psychosocial interventions are unlikely to happen when patients are loaded-up on their cocktails of psychiatric medications.

Since the majority of highly industrialized countries provide antipsychotic and other psychiatric medications for most patients presenting with psychosis, it is unlikely that

Table 1. Symptom-Moderating Effects of Specific Orthomolecular Substances

Potentially improves positive symptoms	Potentially improves negative symptoms	Potentially improves cognitive function
<ul style="list-style-type: none"> - L-lysine - L-Theanine - B-Complex vitamins (especially, vitamins B₆, B₁₂, and folic acid) - Omega-3 essential fatty acids - Vitamin C - Vitamin B₃ 	<ul style="list-style-type: none"> - Glycine (best to combine only with first-generation or the older antipsychotic medications) - NAC - B-Complex vitamins (especially, vitamins B₆, B₁₂, and folic acid) - Omega-3 essential fatty acids - Vitamin C - Vitamin B₃ 	<ul style="list-style-type: none"> - L-lysine - Vitamin B₃

Table 2. Mitigating the Adverse Cardiometabolic and Neurological Effects with Orthomolecular Substances

Potentially improves cardiometabolic effects	Potentially improves TD symptoms	Potentially improves Acute Neuroleptic-Induced Akathisia
<ul style="list-style-type: none"> - Omega-3 essential fatty acids - Vitamin B₃ (must be niacin/nicotinic acid) - Alpha-lipoic acid (to attenuate weight gain associated with atypical antipsychotic medication) 	<ul style="list-style-type: none"> - Vitamin E (D-alpha tocopherol) - Melatonin - Vitamin B₆ 	<ul style="list-style-type: none"> - Vitamin B₆ (high daily doses are only to be used for 5 days)

the antipsychotic treatment imposed during acute psychotic crises is going to change anytime soon. There is a dearth of residential alternatives to hospitalization where patients could receive alternative support in an environment that focuses on meaning, choice, hope, autonomy, and other relevant existential elements, and where the use of antipsychotic medication is minimized or not pre-

scribed at all. Because there currently are no thriving alternatives to hospitalization, what somehow needs to happen is a shift away from enforcing psychiatric medications for life, and a focus on providing short-term psychiatric medication (if determined to be necessary) only to assuage acute psychotic crises. This could then be followed by life-affirming treatments, such as restorative or-

thomolecular regimens and supportive use of psychological therapies, psychoeducation, proper housing, adequate food and access to social services that focus on self-management and personal empowerment strategies.

Conclusion

The mortality for schizophrenics is 15–20 years earlier than the general population.⁵⁹ I contend that the long-term reliance on high doses of antipsychotic and other psychiatric medications given to these individuals result in poorer long-term prognoses and contributes to early mortality. These pills make it very challenging for the aforementioned orthomolecules to lessen psychosis and other psychiatric symptoms, and ameliorate drug-induced neurological damage (if present).

However, as this article points out and as Abram Hoffer reported over his decades-long career, it is possible for orthomolecular regimens to help some patients, particularly those with early-onset schizophrenia. In acute cases, high doses of antipsychotic medications may only be needed for brief periods until patients stabilize at which point they can continue on low-doses of antipsychotic medications while also taking orthomolecular regimens which can gradually help patients recover normal or have near-normal function.

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Competing Interests

The author declares that he has no competing interests.

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