

Orthomolecular Psychiatry: What Would Abram Hoffer Do?

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Abstract *This article provides a practical explanation of orthomolecular psychiatry as practiced by my father, Abram Hoffer, a research psychiatrist and biochemist who dedicated his life to finding a cure for schizophrenia. Even after his death in 2009, Hoffer remains an icon for many people suffering from schizophrenia. The article summarizes the formal clinical trials published by Hoffer's research group in the 1950s and 1960s, and the evolution of his clinical practice after he retired from academic psychiatry in 1967. Its content is based on Hoffer's many publications and conversations I had with him over those many years. Given our close relationship, it's unavoidably biased. Explicitly included are my own interpretations, updates, qualifications and disagreements, as framed by my career as an academic internist and clinical investigator. Key historical and other references are cited at the end of an article that was published in this journal in 2010 but which, unfortunately, lacks the in-text reference numbers.¹ Interested readers may contact me for a properly annotated version. They may also consult an article published by Jonathan Prousky with similar intent to this one but a slightly different slant; it is available on the internet.²*

What is Orthomolecular Psychiatry?

According to Wikipedia (accessed May 26, 2014, and slightly paraphrased), *Orthomolecular psychiatry is based on the assertion that there is an optimum nutritional environment in the body. It uses unorthodox forms of individualized testing and diagnosis to attempt to establish an etiology for each patient's specific symptoms, and claims to tailor the treatment accordingly using a combination of nutrients, dietary changes and medications. In the 1950s, Abram Hoffer was the first major practitioner.*

A number of descriptions of the principles of orthomolecular psychiatry are available on the web page of the foundation that publishes this journal (<http://www.orthomed.org/>). Despite their important conceptual content, these documents don't actually provide much in the way of practical detail about orthomolecular psychiatric

therapy. Regrettably, Wikipedia probably has it right that in recent years, some people have come to use "orthomolecular" as a scientific-sounding synonym for "natural product therapy." In my opinion, the practice of regarding any dietary substance used therapeutically as "orthomolecular therapy" obscures it in ambiguity.

The famous chemist Linus Pauling coined the term "orthomolecular" in a review article published in *Science* in 1968. (Pauling also coined "molecular biology.") Pauling and Hoffer viewed orthomolecular psychiatry as a conceptual paradigm for generating testable hypotheses for treating psychiatric disorders. The notion was to explore the clinical implications of modifying the concentrations of molecules that naturally occur in the body (through diet or biosynthesis) and hence for which regulated metabolic

pathways exist, so as to leverage or restore balance in these pathways. Three decades later, the renowned American biochemist Bruce N. Ames provided strong conceptual support for this paradigm by demonstrating how common polymorphisms in the genes can influence metabolic flux, and how metabolic flux may be modulated by altering coenzyme concentrations; the concept applied particularly well to the B vitamins.³⁻⁶ As another example, the relatively common MTHFR C677T variant of methylenetetrahydrofolate reductase, which increases the risk of defective one-carbon metabolism in people with borderline folic acid deficiency, is strongly associated with mental diseases such as schizophrenia, thus suggesting a role for appropriate folic acid nutrition in their prevention and treatment.⁷ Yet another example is the recent discovery that an important proportion of patients with mild versions of phenylketonuria, a disease of phenylalanine toxicity due to deficient activity of phenylalanine hydroxylase, respond very well to extremely large doses of biopterin, a necessary vitamin cofactor for the enzyme.⁸

Orthomolecular psychiatry's purpose is hypothesis generation, based on a sophisticated understanding of biology, nutrition and brain function. It is not enough to come up with a good idea, not even a brilliant one, however. Hypotheses generated within the paradigm have to be put to the clinical test.

Hoffer's Orthomolecular Psychiatry

The clinical hypothesis Hoffer and his research colleagues tested in the 1950s and 1960s—and which captured the attention of Linus Pauling—involved the use of large doses of the B-vitamin, niacin, as a novel treatment for acute schizophrenia. Their randomized clinical trials suggested that the addition of high-dose niacin (nicotinic acid) to the best available therapy (barbiturates and electroconvulsive therapy) improved the remission rate of people with acute schizophrenia and reduced their risk of relapse.⁹ They published only one short-duration clinical trial of niacin therapy in chronic schizophrenia, with disappointing results. In clinical practice,

Hoffer always combined high-dose vitamin C with niacin and later added other B vitamins, especially pyridoxine (vitamin B₆) and later yet, folic acid. He advocated a low carbohydrate “junk food-free” or “paleolithic” diet, and later became convinced that certain foods and food additives could have important adverse cognitive effects in specific psychotic patients.

Hoffer was among the first North American psychiatrists to realize that schizophrenia is caused by disordered brain chemistry, a radical view in the late 1950s. He and his close colleague, Humphry Osmond, considered that about one third of people with acute schizophrenia may recover spontaneously, and they came to regard their approach of optimized nutrition, lifestyle and certain vitamin supplements as enhancing natural recovery. Patients immediately understood the difference between symptom suppression and recovery. I suspect that the hope and motivation this attitude inspired in patients may have contributed to some of his recovery successes. Recovered patients often reported the life-enhancing effect of simply being asked what they planned to do with their lives after they recovered.

Recovery from schizophrenia is not mentioned in modern psychiatry textbooks nor taught to psychiatry residents, despite the overwhelming evidence for it in the psychiatric literature. The notion of recovery seemingly contradicts popular theories about schizophrenia as a neurodevelopmental disease. More importantly, it creates a serious practical dilemma. One of the great practical challenges of modern schizophrenia care is convincing patients to keep taking their medication. People who suffer more frequent relapses have a worse long-term prognosis (the extent to which this phenomenon reflects cause or effect is not so clear). Psychiatrists want to feel comfortable insisting that their patients stay on antipsychotic medication for life, despite the risk of serious side effects and toxicity, and it is much easier to do so when they are convinced that doing so is indisputably in their patients' interest. But the data indicate otherwise. Prospective

studies of stopping medication provide hints as to which patients are most likely to relapse and which more likely to remain well,^{10,11} but the predictors are far from foolproof. To complicate matters, it is unclear which patients relapse because their underlying disease has flared up or because their brains have become habituated to their antipsychotic drug.¹²⁻¹⁴ If it were publicly acknowledged that a certain proportion of patients who are in remission can indeed go off drugs without relapsing, how much harder would it become to convince people who really need them to continue taking them? It's a complicated business, but the evidence is what it is: some patients will not relapse, presumably and especially when the drug is tapered off very slowly to avoid rebound psychosis.^{12,13} What does all this mean biologically? Hoffer believed that natural recovery from schizophrenia is of central biological importance and highly relevant to clinical practice.

As his views matured, Hoffer came to regard the human brain as functioning both within a social system and a biological one, namely, the physical body. Both systems need respect and looking after. In this regard his views don't seem to differ much from those of Loren Mosher, chief of the Center for Studies of Schizophrenia at the United States National Institute of Mental Health between 1969 and 1980 (see <http://www.moshersoteria.com>) and one of Hoffer's great scientific enemies. Hoffer advocated social support, shelter, respect, supportive psychotherapy, rest, exercise, healthy diet, and avoidance of alcohol, cigarettes and other recreational drugs. Compare this approach with the Mosher-inspired "recovery" model of schizophrenia.¹⁵⁻¹⁷ The chief difference may be that, unlike Mosher, Hoffer paid careful and explicit attention to lifestyle and nutrition. Hoffer would disapprove of the way current schizophrenia recovery paradigms ignore the critical role of physical well-being and sound nutrition in optimum cognitive function. Why, Hoffer would ask, wouldn't these essential contributors to overall good health be at least as important for people who are struggling with a disease

that impairs cognitive function? The diet of many schizophrenic patients is vitamin-deficient,¹⁸⁻²¹ and certain subclinical vitamin deficiencies (especially vitamin C, thiamine, folic acid and cobalamin) are known to adversely affect mood or cognition.

What are the Megavitamins?

Abram Hoffer and Humphry Osmond essentially stumbled upon the niacin treatment for acute schizophrenia. Hoffer's doctoral research at the University of Minnesota dealt with the B vitamins. He was aware that the niacin deficiency disease, pellagra, sometimes manifests as a psychiatric disorder that occasionally requires large doses of niacin to reverse. He read case reports of the effective use of large doses of niacin to treat certain organic brain disorders. Why not try it in acute schizophrenia? At the time they were entertaining this idea, Hoffer and Osmond were working on the theory that the accumulation of a putative, highly reactive oxidative metabolite of adrenaline, adrenochrome, could trigger a neurotoxic reaction manifesting as schizophrenia. Despite recently published claims to the contrary,²² it is now established that adrenochrome is synthesized within the human body and that its administration to humans causes a temporary psychotic state.²³⁻²⁵ What is not so clear is how this metabolite of adrenaline could get into the cortex or subcortex of the brain, when the only nerve terminals known to release adrenaline are located in the brainstem. Perhaps, as Smythies has surmised, as yet unidentified reactive metabolites of the closely related and widely distributed neurotransmitter, noradrenaline, could have neurotoxic effects similar to those of adrenochrome.²³ Hoffer and Osmond wondered whether large doses of niacin (which is metabolized in part by methylation) could limit the availability of methyl groups necessary to convert noradrenaline to adrenaline (it's now clear that such a mechanism is highly unlikely) or, perhaps, that it boosted or sustained neuronal concentrations of the cellular protective coenzyme, NAD.²⁶ They further reasoned that large doses of the

antioxidant vitamin C might prevent adrenochrome from accumulating in the blood and brain. Simultaneously addressing these different potential mechanisms, they treated a number of acutely schizophrenic patients with the combination high-dose nicotinic acid and vitamin C with astonishingly beneficial results. (No doubt these favorable responses were easily detected because the antipsychotic drugs were not available at the time they carried out these trials. The antipsychotic drugs suppress psychosis due to a number of causes and are now the standard of care in this situation.)

Here is a summary of Hoffer and Osmond's megavitamin therapy for acute schizophrenia.

1. Nicotinic acid (commonly known as niacin) is widely available in 500 mg tablets. Start with 500 mg niacin daily after a meal for a few days, then gradually increase the dose at seven day intervals, over four to six weeks, to reach the target dose of 1 gram three times per day.
2. Vitamin C, one gram three times daily right from the start.
3. Pyridoxine 250 mg per day. Later, Hoffer often prescribed a B-50 complex tablet twice per day instead.

Details of Niacin (nicotinic acid) Therapy

Niacin effectively lowers serum triglyceride and LDL ("bad") cholesterol levels while increasing HDL ("good") cholesterol. Niacin is available without prescription, is

covered by health insurance plans, and is inexpensive in any case. Niacin's important nuisance side effect is transient skin flushing and itching. Skin vasodilation, redness (flush) and itching are separate phenomena mediated by the release of different prostaglandins from different skin cells.²⁷ The flush/itching episode subsides after 30 to 45 minutes, and diminishes greatly in intensity (and usually disappears) after a few days of continuing niacin administration (a phenomenon called tachyphylaxis). Flush/itching is maximal at the 500 mg dose. It does not worsen with increasing doses. Sometimes mild flush/itching occurs unpredictably. People with a fair or rosy complexion ("blushers") flush and itch more intensely than people with a swarthier complexion. If a few doses are missed the flush/itching recurs upon restarting it. Two points should be emphasized about this side effect. The first is that it is a nuisance, innocent of danger, for the vast majority of patients, and it is completely reversible. The second is that there are effective strategies for mitigating the side effect while waiting a few days for tolerance to develop (see **Table 1**, below).

Early in his research Hoffer discovered that a large proportion of people with schizophrenia do not flush after niacin administration, a phenomenon that has since been widely confirmed and is under active investigation using a standardized niacin-impregnated skin patch which induces a localized area of reddening in most normal

Table 1. How to Mitigate an Episode of Niacin-induced Flush/itch

Take niacin with or after food, with a glass of cold water. Do not take niacin on an empty stomach. These actions prevent rapid gastric absorption and greatly reduce the intensity of the flush/itching.

Take 80 mg of aspirin (or 325 mg if the lower dose doesn't work) half an hour before the morning dose of niacin. Have a good reason for taking niacin and a positive attitude about its potential neuroprotective and healing effect. The flush can be regarded favorably, as a sign it is "working." Enjoy the pleasant, relaxing post-flush sensation.

people, but a lesser or absent response in people with schizophrenia. The no-niacin-flush phenomenon may be the only confirmed biological marker we currently have for “schizophrenia.” The mechanism is under investigation. Many tissues, including certain skin cells, fat cells, and neurons, have been found to express “niacin” receptors. There is some suggestion that the expression (or regulation) of these receptors is abnormal in predictable areas of the brain of schizophrenic people but not people with other forms of mental illness.¹

It is essential to fully explain the niacin flush/itch phenomenon, its transience, and how to mitigate it, to anyone contemplating niacin therapy. Systematic studies show that most uninformed patients do not tolerate this side effect^{28,29} whereas most appropriately informed and counseled ones tolerate it well.³⁰

If there was insufficient or no response after three or four months, Hoffer would increase the niacin dose up to about six grams per day (sometimes higher). He claimed to get responses at the higher doses that were not obtained at lower doses. But he never published these data except anecdotally.

Niacin Toxicity

Properly informed and appropriately motivated people tolerate high-dose niacin without problem, but anyone who prescribes niacin has to be aware both of its innocent side effects and its rare potential for adverse effects and toxicity. Several recent reviews are available and should be consulted.³⁰⁻³³ Here is a summary of the important features.

Liver toxicity As with all lipid-lowering agents (such as the now very widely prescribed statins) it is obligatory to measure serum liver enzyme levels prior to commencing niacin therapy and repeat them after about six or eight weeks of therapy. (The risk of liver function abnormalities is greater when niacin and a statin are prescribed in combination.) Any liver function abnormalities found to be present at baseline require a diagnosis. For example, Wilson’s disease causes hepatitis, but its first symptom can be

psychosis. Many people with a psychiatric disorder overuse alcohol, and even ordinary alcohol consumption will transiently elevate liver transaminases. In our current obesity epidemic (including obesity induced by antipsychotic drugs), fat accumulation in the liver can induce non-alcoholic steatohepatitis (NASH) that is manifested by elevated serum liver enzymes.

The niacin dose is increased gradually to prevent liver enzyme elevation. Very occasionally a patient’s serum liver enzyme level will rise, but as long as the increase is to less than three times the upper normal limit and the patient feels well, niacin can be continued with continued monitoring; in most cases the enzyme level will return to normal on its own. Clinical liver toxicity is very rare with ordinary niacin.³²

Hyperacidity Niacin stimulates stomach hydrochloric acid secretion, presumably by activating or sensitizing gastric H₂ receptors. The resulting hyperacidity can be troubling for many patients, and this is another important reason for taking the vitamin after meals. If necessary, the H₂-blocking drugs ranitidine or famotidine can be used temporarily, or long-term.

Hyperuricemia Niacin very slightly increases serum uric acid concentrations (it competes with urate for secretion by the renal tubules). Patients at high risk could experience an attack of gout.³⁰

Nicotinamide as an Alternative to Niacin

Some people simply will not tolerate niacin due to the intensity of flush/itching (I have even rarely seen urticaria). People with aspirin-exacerbated respiratory disease (a triad of aspirin allergy, nasal polyps and asthma) can develop severe nasal congestion and headache after niacin. When niacin proved to be unacceptable, Hoffer prescribed nicotinamide, a different form of vitamin B₃ that does not cause flush/itching (and does not improve the serum lipid profile). The clinical trial evidence that nicotinamide is beneficial in acute schizophrenia is weaker than for niacin, consisting as it does of a sin-

gle double-blind clinical trial that indicated equal superiority of niacin and nicotinamide over placebo. The maximum daily dose of nicotinamide is 3 g, because, unlike niacin, larger doses can cause nausea and liver toxicity. There is current interest in the use of nicotinamide as a neuroprotective agent. Its safety and lack of side effects are well documented.³⁴

Slow Release Niacin

Hoffer occasionally prescribed extended release niacin (so called “no-flush” niacin), but I recommend against it. First, some of the products on the market may not be reliably absorbed from the gastrointestinal tract, or, if absorbed, release their niacin. One commonly used extended release product, inositol hexanicotinate, appears to be absorbed but has questionable efficacy. Second, unlike ordinary niacin, slow release products may induce liver toxicity. Readers may consult recent reviews.^{30,32,33} Niaspan is a well-studied, safe, formally approved extended release product available on prescription in Canada and the United States for the indication of lipid lowering. The maximum recommended dose is two grams at bedtime. Higher doses are not necessarily dangerous, but they have not been verified to be safe, and prescribing them would be off-label.

Other B Vitamins

Hoffer prescribed pyridoxine (vitamin B₆) partly because many enzyme activities can be increased with pharmacologic doses of this B-vitamin enzyme cofactor, but mostly because colleagues anecdotally reported good clinical results (often together with zinc). I never saw a suitable presentation of the evidence supporting its use. Doses greater than 250 mg/day are not recommended because of rare reports of sensory neuropathy after long-term use, although typically in doses closer to 2 g/day. People with the serious metabolic disease, homocystinuria, commonly take very large doses of pyridoxine with great benefit and no reported toxicity. On balance, given the uncertainty of benefit and the small but real risk of

toxicity, it is prudent simply to prescribe two B-50 complex vitamin formulations, each of which contains 50 mg of most of the B vitamins, including pyridoxine (but not more than 1 mg folic acid).

Vitamin C

Hoffer and Osmond prescribed 1 g vitamin C three times per day. I am unconvinced that this much is necessary – perhaps 500 mg twice a day would be as effective – but it is safe, except possibly for people with a documented history of oxalate kidney stone. Nevertheless, since their clinical experience was based on this regimen, I continue to recommend it. Vitamin C has two advantages. First, it reliably lowers uric acid concentrations³⁵ and hence could mitigate a potential side effect of niacin. Secondly, there is promising evidence that vitamin C protects the stomach from the adverse effects of aspirin and presumably other NSAIDs.³⁶

Tailor Therapy, but Don't Make it Too Complicated

Wikipedia is correct that Hoffer individualized therapy. Patients who tolerated 3 g niacin per day but failed to respond might be prescribed 6 g per day and, rarely, even more. In addition, he emphasized sound general nutrition individualized for each patient. Patients with iron deficiency would have their iron deficiency corrected, for example. Once the fish oils came on the scene he did not hesitate to prescribe eicosapentaenoic acid (EPA) in a dose of 2 g per day taken together with a fat-containing meal to enable absorption. Given the abundance of vitamin D receptors in the human brain, he would not hesitate to prescribe vitamin D (or sunlight) to a patient with vitamin D insufficiency. (Vitamin D deficiency has been linked to depression, but I have not seen evidence that it triggers or exacerbates psychotic disorders.) Intriguing preliminary but rigorous and biologically plausible data suggest a benefit of the antioxidant supplement N-acetylcysteine, both in schizophrenia and in obsessive-compulsive states like hair-plucking.³⁷⁻⁴⁰

It is biologically and clinically plausible to recommend natural vitamin E 400 IU twice daily (with food to enable absorption) to prevent tardive dyskinesia. There is strong but inconclusive evidence that high-dose vitamin E mitigates existing tardive dyskinesia.⁴¹ Why not, then, prescribe the vitamin to prevent this devastating toxic effect of antipsychotic drugs from developing in the first place? Vitamin E may have a role in mitigating NASH.⁴²

Food intolerances There is evidence that people with coeliac disease, which is caused by an intestinal allergy to gluten, are at increased risk of schizophrenia.^{43,44} Gluten can cause extra-intestinal manifestations in the skin or brain in people with coeliac disease.⁴⁵⁻⁴⁷ Medical understanding of the spectrum of gluten intolerance has entered an era of great uncertainty and shifting terminology^{48,49} that goes beyond the scope of this article. Suffice it so say that there is now good evidence that adverse reactions to gluten are not limited to people with proven coeliac disease.^{48,50} A trial gluten-free diet is therefore reasonable in people with suggestive symptoms even when their total IgA level is normal and their IgA antitissue transglutaminase antibody titre is low. Contrary to what most general physicians realize, there is very good evidence that certain food additives or ingredients can adversely affect behavior in children with or without a behavioral disorder.⁵¹ No systematic evidence, one way or the other, has been published in adults.

How much tailoring is too much? Much is speculated, more is unknown, and little is clear. There is an understandable tendency to load the patient up with as many goodies as possible. I recently saw a patient with schizophrenia who, after paying thousands of dollars for specialized blood and hair tests, was prescribed a protein-rich diet, a gluten-elimination diet and a large number of supplements including niacinamide, zinc, copper, slippery elm, lipoic acid, EPA, iron, and vitamin C. The program didn't work for this particular patient because it was simply overwhelming. I don't have an easy answer

for this dilemma, but common sense suggests making the prescription as simple and replicable as possible. Prescribe what Hoffer prescribed and see what happens. The patient has to understand the program and its implications, want to go for it, and be able to follow through with it. Be on the lookout for what seems to help the most. It's uncertain, meticulous work, with no guarantee of success. The only way to sustain such an effort is to care about the patient and sustain unbiased intellectual curiosity.

Therapeutic Goals

After the antipsychotic drugs became available Hoffer used them, but judiciously. He aimed for the lowest effective dose ("as little as possible, as much as necessary") while colleagues opted for the highest tolerated dose to minimize the risk of relapse. The following treatment philosophy would be in line with Hoffer's approach:

The patient should be in the best condition on the lowest effective dose of appropriate antipsychotic medication.

Orthomolecular psychiatry is neither proven nor refuted, so practice evidence-based medicine. In the situation when the balance among benefit, risk and disadvantage cannot be confidently estimated, the rules of evidence-based medical practice require the therapist to explain the uncertainty, the potential benefits and risks of the proposed treatment and ensure that the decision as to whether to proceed, or not proceed, is consistent with the patient's attitudes and preferences.^{52,53} In light of the well-documented inadequacies of standard antipsychotic drug therapy^{54,55} and the lack of evidence that polypharmacy is any better,⁵⁶ the balance of uncertain benefit versus minimal risk could well tip in favour of orthomolecular therapy for certain, suitably assessed, informed and motivated patients. Indeed, proceeding with the lifestyle approach alone can only benefit patients, including patients with antipsychotic drug-induced obesity and hyperlipidemia. Rational orthomolecular psychiatric practice, as described here, is consistent with the principles of evidence-

based medicine.³⁹

Allow at least three months for a beneficial effect to occur before increasing the niacin dose or abandoning it, and be willing to wait much longer than this for patients with chronic schizophrenia.

If the patient is in complete remission, do they really want to embark on what is a complex and demanding change in their lifestyle? The answer is likely to be “no” for many people. Are social support structures in place? The patient should be able to articulate persuasively why they want to go proceed with the program. The orthomolecular therapist’s responsibility is to make sure the program is well explained and understood, and that it is feasible, safe and inexpensive for this particular patient. Decisions about tapering the antipsychotic drug are between the patient and their psychiatrist. Dose tapering should never commence before at least six months on the full lifestyle and vitamin regimen. The aim of therapy is remission on the lowest necessary dose of antipsychotic medication. Hoffer defined success as complete remission on the smallest necessary dose of antipsychotic drug. For some patients, that dose may be zero.

If the patient has residual positive symptoms attributable to their disease, it makes sense to monitor them (intensity and frequency) as signals of whether the lifestyle/diet/vitamin approach is actually helping. The therapist should objectively record the patient’s symptom status. Hoffer, an experienced psychiatrist, always based his decisions on clinical judgment, but he also used, and advocated, the Hoffer Osmond Diagnostic (HOD) test, a self-report card-sorting test that was later succeeded by a more sophisticated test called the Experiential World Inventory.^{57,58} Both tests survey the patient’s perceptions and thought processes. The practical limitation of both tests is that they are not standardized, validated, nor widely used. I recommend adding or substituting standard, widely used symptom scales whose results will be understood and credited by conventional psychiatrists.

Which Patients Respond and How Fast?

The existing clinical trial evidence suggests that niacin improves acute schizophrenia (i.e. less than two years chronicity). The negative clinical trials that Wikipedia refers to as refuting niacin therapy were carried out in chronic schizophrenic patients, the majority of them institutionalized and deteriorated. Hoffer told me he sometimes saw rapid and dramatic improvements in patients with acute schizophrenia but sometimes had to wait months to see the benefit. Generally, he told me, patients with chronic schizophrenia improved only very slowly or not at all. But he never gave up on any patient.

How could I forget Luella R, a young woman with chronic refractory schizophrenia who helped look after my brother, sister and me when we were small children! My father describes her (giving her the pseudonym Mary Jones) in one of his last books.⁵⁹ Luella would have spent her entire life in the back ward of a chronic psychiatric hospital had Hoffer not brought her to live in our house, in a therapeutic milieu. She slowly but entirely recovered in this environment, but only after she was treated with niacin.

Did Hoffer’s Patients Have Schizophrenia?

Hoffer’s therapies focused on using niacin, among other nutrients, to treat what he diagnosed as acute schizophrenia based on an unaccepted test. In 1973, a task force of the American Psychiatric Association examined niacin monotherapy of patient populations with chronic schizophrenia and bipolar disorder and rejected the practice along with the reliability of Hoffer’s diagnostic approach. (Wikipedia)

It has been claimed—as recently as a year after Hoffer’s death²²—that the recoveries and sustained remissions reported in his randomized clinical trials are bogus because the patients enrolled in them didn’t have schizophrenia, but rather a variety of other conditions he and Osmond falsely identified as schizophrenia using the HOD test. This is simply untrue. Hoffer always used standard clinical diagnostic methods to diagnose schizophrenia. He advocated using the

HOD test to follow its clinical progress. The patients in their formal clinical trials were not enrolled by Hoffer or Osmond, but rather by other collaborating psychiatrists, many of them skeptical, using standard diagnostic methods.⁶⁰

This is not to claim that in later years Hoffer refused to treat patients suffering from psychotic disorders that might or might not later turn out to be schizophrenia. He tried to help every patient. He would normally diagnose schizophrenia in a patient who manifested delusions, hallucinations, disorganized or blocked thinking, and negative symptoms such as inertia, lack of enjoyment, and lack of social interest.

Does Orthomolecular Psychiatry Work?

In 1973, a task force of the American Psychiatric Association examined niacin monotherapy of patient populations with chronic schizophrenia and bipolar disorder and rejected the practice. (Wikipedia)

Regrettably, the APA's 1973 Task Force Report 7, Multivitamin and Orthomolecular Therapy in Psychiatry, is no longer available.⁶¹ Task Force Report 7 contains some cogent criticisms, but it is seriously marred and to a considerable extent discredited by its unashamedly hostile, scornful bias. The Task Force Report correctly concluded that there was no good published evidence that high-dose niacin is useful in chronic schizophrenia, but failed to concede the evidence pertaining to niacin treatment of acute schizophrenia. More evidence is certainly necessary, but the barriers to obtaining are insurmountably high at the present time.¹ A particularly important problem in schizophrenia is heterogeneity.⁶² Schizophrenia may represent a nonspecific cognitive dysfunction with more than one cause.

A most interesting clinical trial of niacin therapy was published in 1973 by a respected psychopharmacologist and clinical trial specialist, J.R. Wittenborn. This United States National Institutes of Health-funded trial compared the clinical effects of standard antipsychotic therapy with intensive social support versus the same therapy supple-

mented with 3 g per day of niacin.⁶³ Study participants were enrolled at the time of admission to the Male Admission Ward of the New Jersey State Hospital at Marlboro with a diagnosis of an episode of schizophrenia, and closely followed on treatment for two years. As with most trials in schizophrenia, the dropout rate was very high (only 75 of the 140 patients originally enrolled completed the protocol, making intention-to-treat analysis impossible) and baseline randomization was imperfect. The patients assigned to supplemental niacin were significantly more chronic (an average of 4.8 years had transpired since their first serious psychotic episode, whereas only 3.0 years had transpired in the control group). Basing his results on the outcome of the 86 patients who remained in the study for at least 18 months, Wittenborn found that psychiatric rating scales, social adjustment, self-report, and medication data were similar in both treatment groups. While cautioning that the data analysis was continuing, Wittenborn concluded that his study had failed to show that niacin was a useful add-on therapy for this kind of schizophrenic patient.⁶³ The following year Wittenborn published his final analysis. It indicated that people whose interpersonal relationships had been relatively normal prior to developing schizophrenia responded well to niacin, whereas people in the control group with the same pre-morbid characteristics did not improve.⁶⁴ Such people accounted for one-third of the patients in the study. Acknowledging the post-hoc nature of his analysis, Wittenborn recommended that a new clinical trial be carried out to explore the important implications of his findings. His recommendation was ignored. His second article is never cited.

How Can We Find Out Which Patients Will Respond To Orthomolecular Therapy?

The amount and kind of randomized clinical trial evidence that orthomolecular psychiatry reliably benefits most patients with acute schizophrenia is, at the present time, insufficient to justify its routine pre-

scription. The likelihood of obtaining the kind of clinical trial evidence necessary either to establish or refute it is almost zero, at least for the foreseeable future. Randomized clinical trials, even of single drugs, are very difficult to carry out in schizophrenia. The kinds of clinical trials necessary to properly evaluate orthomolecular therapy would be much more difficult to fund and carry out even if funded.¹ Prompt and easy detection of a favorable response to orthomolecular therapy will be confounded by the symptomatic effectiveness of the antipsychotic drugs, which are, as they should be, the standard of care. (Imagine trying to test a potentially curative treatment for chronic headache in people who continue taking large and risky doses of aspirin with moderate symptom control.) The validation or refutation of Hoffer's orthomolecular therapy will eventually come in the form of fundamental breakthroughs in our understanding of the biology of schizophrenia. In the meantime, is there anything that can be done clinically? What comes to mind, and is available to any suitably trained and motivated therapist, is careful clinical observation and the preparation and publication of high quality, sophisticated case reports. Even more important would be consecutive case series to eliminate selection bias. Well presented case reports are anecdotes, but that doesn't make them unimportant if something can be learned from them.^{65,66} Evidence-based medicine is well served by clinical evidence from uncontrolled observations when the effect is large, unmistakable and well-documented.⁶⁷ Dramatic narratives of recovery, including recovery from schizophrenia,^{16,65,66,68,69} are appropriate and can be influential. I hope that well-documented and well-told case reports could be published in this journal.

Writing these lines, I remember an interview I had many years ago with a young man diagnosed with schizophrenia. I was home from university for the summer, and my father asked me to go through some of his clinical charts, contact the patient, and get longer term follow up information. This young man, now a high school senior, was

completely normal on niacin. During our conversation he remarked that when he had to write essays for school he would stop taking the niacin for a few days because the loosening of associations that followed soon after improved his creative writing. I found this unembellished narrative, from a down-to-earth, intelligent young man, electrifying. It was authentic. Admittedly, it was merely the fragment of an anecdote. It might just have been a "placebo effect."

Conclusions

The people most likely to benefit from orthomolecular psychiatric therapy have acute schizophrenia, and among them, those who have a history of a good pre-morbid psychological adjustment. These are the very people most likely to experience a natural recovery. This is not to say that people with chronic schizophrenia cannot benefit, but acceptable evidence is lacking. Hoffer's experience was that improvements can take a long time to come about. Depending on the patient's situation, attitudes and preferences, one would use the basic regimen of niacin, vitamin C, and B complex 50, normal vitamin D status, a junk-free diet, avoidance of stimulants and drugs, and cognitive therapy, personal respect, and the lowest effective dose of antipsychotic drug. When feasible, a plausible interpretation of the evidence suggests that 400 or 800 IU vitamin E (with food to enable absorption) is a prudent measure that might prevent tardive dyskinesia. An additional promising possibility is N-acetylcysteine in a dose of 1 g twice daily. Orthomolecular therapy is off-label, so the patient must be fully informed about the uncertainty of the evidence supporting it. Baseline disease status should be measured at baseline and during therapy. The symptom rating scales drug companies are required to use to obtain regulatory approval for their products have questionable relevance to real-life experience. More important are the patient's evaluation and objective information of how they are doing. Hoffer's criteria for success were normal perception and thought, normal social relationships, full employment, and paying income tax.

Competing Interests

The author declares that he has no competing interests.

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