Isr J Psychiatry Relat Sci Vol 45 No. 1 (2008) 3–10

Vitamin Therapy in Schizophrenia

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Abstract: Schizophrenia is a devastating and poorly understood disease for which the only accepted therapy is non-specific antipsychotic and anti-seizure medication. This article summarizes the evidence that certain vitamin deficiencies likely worsen the symptoms of schizophrenia, and the evidence that large doses of certain vitamins could improve the core metabolic abnormalities that predispose some people to develop it; it recounts the history of a controversial vitamin-based therapy for schizophrenia called orthomolecular psychiatry; and it concludes by advocating a process for discovering promising new schizophrenia therapies that involves small, carefully conducted clinical trials of nutrient combinations in appropriately selected patients.

It is dismaying that well into the 21st century schizophrenia remains a highly prevalent, devastating and poorly understood disease for which the only accepted therapy is non-specific antipsychotic and anti-seizure medication. Fresh approaches, even unconventional ones, should be welcomed for study by the psychiatric community if they are biologically plausible and non-toxic. This article summarizes the evidence that certain vitamin deficiencies can worsen the symptoms of schizophrenia, and the evidence that large doses of certain vitamins could improve the core metabolic abnormalities that predispose some people to develop it; it recounts the history of a controversial vitamin-based therapy for schizophrenia called orthomolecular psychiatry; and it concludes by advocating a process for discovering promising new schizophrenia therapies that involves small, carefully conducted clinical trials of nutrient combinations in appropriately selected patients.

Schizophrenia is a chronic disorder of brain function that affects perception, cognition, motivation and behavior. Its predisposition, precipitating causes and pathophysiology are very poorly understood, but, as in all chronic diseases, likely to be strongly influenced by psychological factors. Lacking biological insight, psychiatrists diagnose schizophrenia purely from its clinical presentation, a practice that is known be highly unsatisfactory but may be of some value in identifying patients whose symptoms are predominantly "positive" or "negative." For example, it has been reported that patients with a history of poor pre-morbid psychological adjustment and more neuropsychological and neurological abnormalities have a worse prognosis (1).

People in the early stage of schizophrenia generally respond better to antipsychotic drug therapy than those who have had the disease for many years, and early intervention is currently believed to prevent the disease from progressing to a treatment-resistant stage (2). These drugs control psychosis with varying degrees of success, but their toxicity and often disabling side effects reduce medication adherence and contribute to the high relapse rate typical of schizophrenia (3). Some people with well-diagnosed schizophrenia have spontaneous remissions and no longer require antipsychotic drugs; the explanation for these favorable outcomes is unknown (4).

Psychiatrists attempting to discover an etiology-based therapy for schizophrenia may take two general approaches. The first is subgroup analysis of large randomized clinical trials. Unfortunately, subgroup analysis is difficult and notoriously unreliable, and the validity of even the overall analysis of large randomized clinical trials is questionable when their eligibility criteria exclude much of the patient population, only a small fraction of eligible patients participate, and a large fraction of participants withdraw from the study prematurely (3). The second approach is for the interested and open-minded psychiatrist to gather clinical and biological information

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on the lookout for promising leads, as described later in this article.

Vitamin Deficiencies and Vitamin Therapy in Schizophrenia

It is currently popular to regard schizophrenia as a "multiple-hit" neurodevelopmental disorder; equally plausible is the older hypothesis of a toxic psychosis triggered by an abnormal endogenous metabolite. Organic brain disorders indistinguishable from schizophrenia may be induced by certain drugs and by neurological, metabolic, inflammatory and infectious diseases (1). Such disorders account for approximately 5% of cases initially diagnosed as first-episode schizophrenia by expert psychiatrists (5). Wilson's disease, unrecognized adult phenylketonuria (6), pellagra and celiac disease (7) can induce brain disorders indistinguishable from schizophrenia. A patient with celiac disease and classic schizophrenia with typical SPECT scan abnormalities had complete resolution of both diseases after being placed on a gluten-free diet (8). Although known metabolic disorders and neurologic injury only rarely cause clinical schizophrenia, their very existence is good reason to search for the abnormal molecules, enzyme activities, and markers of brain injury that may eventually reveal its cause or causes.

In 1968 the renowned chemist Linus Pauling published an article in *Science* entitled Orthomolecular Psychiatry in which he described a biochemical model for investigating nutritional therapies for mental diseases (9). Pauling defined orthomolecular psychiatric therapy as the treatment of mental diseases by providing the optimum molecular environment for the brain, especially the optimum concentration of substances normally present in the body. Examples of orthomolecular therapy include dietary phenylalanine restriction in phenylketonuria, high-dose pyridoxine therapy in pyridoxine-responsive variants of homocystinuria, and the treatment of the psychosis caused by pellagra with niacin. The notion that the brain is affected by its molecular environment is hardly controversial; what made Pauling's article novel was that it laid out a conceptual framework for generating hypotheses about the pathogenesis and treatment of mental diseases. He identified a number of mechanisms by which variations in the concentration of a vitamin or other naturally-occurring molecule that serves a metabolic regulatory role could improve brain function, such as by changing an enzyme's catalytic activity through a shift in the equilibrium between coenzyme and apo-enzyme.

An example pertinent to my own research may be cited. For unknown reasons, plasma homocysteine concentrations are markedly increased in most people with end-stage renal disease. We and others recently showed that parenteral vitamin B_{12} therapy greatly increases the serum cobalamin concentrations of hemodialysis patients and can virtually eliminate their hyperhomocysteinemia. It is known from cell-culture studies that in very high concentrations cobalamin greatly increases the activity of the cobalamin-dependent, homocysteine-metabolizing enzyme, *methionine synthase*. Accordingly, we have suggested that the hyperhomocysteinemia of renal failure is largely due to uremic inhibition of *methionine synthase* which can be overcome *in vivo* by therapeutically increasing the tissue concentration of its coenzyme (10).

Vitamin therapy could benefit people with schizophrenia by preventing or reversing the symptoms of vitamin deficiency disease, or by normalizing disordered brain metabolism when administered in doses greater than required to prevent deficiency. Since the diet of people with mental illness is often extremely poor, it is quite likely some of them suffer from vitamin deficiencies which could worsen their already disturbed brain function. Simple correction of unrecognized nutrient deficiencies could explain the improvements reported in mentally ill patients and prison inmates administered standard vitamin supplements (11, 12).

Modern advances in molecular biology generally support the concept of orthomolecular psychiatry as proposed 40 years ago (9). As many as one-third of pathologic gene mutations are now considered to cause clinical disease by decreasing the affinity of an enzyme for its coenzyme or substrate, reducing the enzyme's catalytic activity (13). Many single-nucleotide polymorphisms could also reduce catalytic activity by decreasing coenzyme-apoenzyme binding, including the binding of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide-phosphate (NADP), the cofactors syn-

thesized from dietary niacin and niacinamide (13). In such situations the impairment could, in principle, be at least partly remedied by raising intracellular cofactor concentrations with high-dose vitamin therapy. Evidence has steadily accumulated that cellular NAD, the concentrations of which can be modified by niacin or niacinamide administration, plays critical roles in metabolic regulation and repair (14). In pharmacologic doses niacinamide is neuroprotective (15). Such effects are potentially relevant to the pathogenesis or mitigation of schizophrenia. An autosomal dominant genetic disease characterized by psychiatric symptoms, and specifically cured by niacinamide, has been described (16).

The clinical literature on vitamin therapy in schizophrenia is reviewed below.

Folic Acid

Subclinical folic acid deficiency increases plasma homocysteine concentrations, causes congenital birth defects, depression and other psychiatric symptoms, and reduces the effectiveness of antidepressant drugs (17, 18). It is logical to predict that patients with schizophrenia and subclinical folic acid deficiency would benefit from prevention and treatment of folic acid deficiency.

The prevalence of folic acid deficiency decreased in Canada and the United States after food fortification was introduced in 1998, but important population subgroups continue to consume inadequate amounts of this vitamin. Plasma homocysteine concentrations are increased in some patients with schizophrenia (19–22). It is uncertain whether, and in whom, this abnormality is due to inadequate folic acid or vitamin B_{12} intake, abnormal folic acid or vitamin B_{12} metabolism, or both (22–24). One of the dividends of modern molecular biology is the ability to capitalize on the "experiment of nature" produced by Mendelian randomization by testing whether a specific genetic abnormality contributes to the pathogenesis of a disease (25). Recent meta-analyses of such trials indicate that homozygosity for a common polymorphism in folic acid metabolism increases the risk of developing schizophrenia and depression (26). Clinical reports have described abnormal folic acid and vitamin B_{12} metabolism in some people with schizophrenia (22). A genetic defect in folic acid metabolism has been shown to cause a schizophrenic syndrome (27). The addition of 15 mg/day of methylfolate to standard psychiatric therapy improved the clinical and social recovery of patients with acute schizophrenia (28, 29).

Ascorbic Acid

Chronic ascorbic acid deficiency leads to scurvy, a fatal hemorrhagic disorder due to defective capillary collagen synthesis in the absence of ascorbic acid. Plasma ascorbic acid concentrations fall to scorbutic levels within four weeks of severely restricted intake, but because of collagen's slow turnover rate the hemorrhagic manifestations usually appear only after several more weeks of deficiency. Clinical scurvy is preceded by fatigue, lassitude and personality change (30, 31) which could well exacerbate a neurologic disease like schizophrenia. Ascorbic acid plays a critical role in the brain, where it is an antioxidant and reducing agent essential for the activity of several enzymes and is involved in neuronal regulation (32–36).

Ascorbic acid deficiency is well known in chronic schizophrenia (37) and regrettably is not a relic of the past, having been observed in approximately one-third of the patients in a modern British mental hospital (38). This high prevalence of ascorbic acid deficiency is not surprising, for people with schizophrenia commonly forego fresh fruit and vegetables in favor of cigarette smoking, a practice which increases the ascorbic acid requirement (35).

It is plausible that the pathologic process responsible for schizophrenia could increase ascorbic acid utilization (39, 40). The acute-phase metabolic response to an inflammatory disease increases metabolic clearance of ascorbic acid and reduces its plasma concentration, sometimes to undetectable levels (41). One can test for increased metabolism or intracellular depletion of ascorbic acid by administering a standard dose of the vitamin and determining the resulting plasma concentration or urinary excretion profile. Ideally the test should be performed before and after a period of known adequate intake. Such tests have yielded mixed results in chronic schizophrenia, and no general conclusion can be drawn from them. No studies have been carried out in acute schizophrenia. Recent randomized

clinical trials have shown that 3 g per day of ascorbic acid reduces biological and subjective indices of stress in healthy young adults (42, 43), and the beneficial effect could be as great or greater in schizophrenia. Two double-blind randomized clinical trials (37, 44), an open trial (45) and a case report (46) indicate that the symptoms of chronic schizophrenia can be ameliorated by high-dose ascorbic acid therapy. No studies have been carried out in acute schizophrenia.

Niacin

Vitamin B_3 administered either as niacin (nicotinic acid) or its amide, niacinamide, prevents and cures pellagra, a deficiency disease characterized by photosensitivity dermatitis, glossitis, diarrhea, and an organic brain syndrome that ranges in its presentation from stupor to a psychosis indistinguishable from schizophrenia. In the 1950s and 1960s, a psychiatric research team in Saskatchewan carried out double-blind randomized clinical trials that demonstrated an important benefit from the continuous daily administration of 3 g of niacin and 3 g ascorbic acid to patients with acute schizophrenia. The clearest and most important benefits were the elimination of psychotic symptoms and the prevention of relapses (47–51).

The Saskatchewan researchers reported that, unlike acute schizophrenia, chronic schizophrenia was unresponsive to the treatment, at least within the time frame of formal clinical trials (52), and that some patients with acute schizophrenia required 6 g per day or more of niacin to control their symptoms (48, 53). They observed that niacin mitigated or curtailed the temporary psychosis produced by LSD and adrenochrome (54, 55), the latter molecule being an unstable product of catecholamine oxidation which they proposed as a neurotoxin capable of causing schizophrenia, and which remains a viable candidate for this role (33, 36, 55–59). Although normal people experience skin flushing upon first exposure to niacin in doses of 250 mg or more, they found that patients with schizophrenia tend not to flush (47, 48). D. F. Horrobin later capitalized on this observation to suggest that the presence or absence of the niacin flush can identify biochemical subtypes of schizophrenia (60). In a side-discovery, they discovered that niacin is a potent cholesterol-lowering agent; niacin is now widely prescribed for this purpose (61).

Despite its publication in mainstream research journals, niacin-ascorbic acid therapy for schizophrenia was ignored by academic psychiatrists. Dating from the mid-1960s, many practicing psychiatrists and primary care physicians began to include niacin and ascorbic acid in a multi-faceted, empirical therapy that included other micronutrients (especially pyridoxine, zinc, and essential fatty acids), and a "junk food free" low-carbohydrate diet, as well as test exclusions of certain foods such as dairy or wheat, always in combination with the best pharmacotherapy available. High rates of sustained clinical remission were claimed in case reports and case series (53, 62, 63). Empiric approaches to clinical therapy are in keeping with the principles of evidence-based medicine and patient-centered care. Different classes of antipsychotic, antidepressant and antiepileptic drugs are commonly combined to eliminate psychotic symptoms, even when the specific combinations have not been validated in controlled trials. In the case of orthomolecular psychiatry, however, the individual components of the therapy were not previously validated by randomized controlled trials, nor, given their variety, would testing be easy. It is difficult to complete controlled clinical trials of even simple pharmacotherapy in schizophrenia.

The "megavitamin" treatment for schizophrenia flared into open controversy after Pauling's article on orthomolecular psychiatry appeared in the world's leading scientific journal (9). Shortly afterwards a prestigious American publishing house published an academic book, co-edited by Pauling, with the same title (64). In 1968 the Canadian Mental Health Association funded a series of small clinical trials aimed at exploring the promise of the vitamin therapy approach. The American Psychiatric Association (APA) commissioned a task force to investigate, and in 1973 published the report of its findings (65). In my opinion, the main purpose of the report was to discourage psychiatrists from taking seriously what its authors clearly regarded as an unproven and implausible approach to schizophrenia therapy. Using dismissive language, they represented the biological and clinical evidence with a negative bias, and selectively quoted statements by orthomolecular psychia-

try researchers in a way that portrayed them in a negative light.

Apart from its well-intentioned but negative slant, the APA report may be criticized for failing to address the possibility that negative clinical trials in chronic schizophrenia may have little or no bearing on a treatment's effectiveness in acute schizophrenia. One trial cited as negative in the task force report is of interest because it enrolled ambulatory patients rather than chronically hospitalized ones, included more participants than previous trials, and followed them for at least 18 months. Although beyond the early stage of schizophrenia, the participants were considerably less chronic than in any previous independent trials: patients in the control group had been sick an average of 3 years, whereas those who received the active treatment — niacin 3 g per day, without ascorbic acid — had been sick for 4.8 years. Overall there was no statistically or clinically significant difference in outcome between the treatment groups (66), but in a subsequent subgroup analysis it was found that niacin-treated patients with a premorbid history of good psychological adjustment improved whereas corresponding patients in the control group did not. Clinical trials were advocated to explore the possibility that patients with a history of strong interpersonal commitments improve with niacin therapy (67). These clinical findings and the recommendation for further research were not mentioned in the APA report, nor in a later review of vitamin treatment in schizophrenia published in the *Canadian Psychiatric Association Journal* (68–70); it remains ignored in the literature. The editor of the *Canadian Psychiatric Association Journal* published a commentary critical both of the proponents of orthomolecular psychiatry, for taking their treatment to the public before it had been accepted by the psychiatric establishment, and its attackers for not conceding that the vitamin therapy remained untested in acute schizophrenia. He regretted the political turn in what might have been a useful scientific exchange (71).

Current views about schizophrenia are in keeping with the notion that patients in the early stage of the disease may respond to a therapy that is ineffective after it has progressed to a fixed chronic state. High-dose niacin, widely used to treat hyperlipidemic conditions (61), is safer and freer from side effects than conventional antipsychotic drugs. Modern investigators, using a quantitative skin patch technique, have confirmed that patients with schizophrenia tend not to flush when exposed to niacin (72–74). A recent report suggested that patients with first-episode schizophrenia tend not to flush, whereas those with the established disease flush normally, suggesting a measurable metabolic difference between different stages or types of schizophrenia (74). The possibility remains to be tested that resistance to the niacin flush indicates patients more or less likely to respond favorably to niacin therapy.

There is recent interest in the possibility that large doses of the long-chain fatty acid, eicosapentaenoic acid, can ameliorate the abnormal biochemistry responsible for schizophrenia. The background and biological rationale for this therapy have been described (75, 76). A recent review dealing with its specific application in acute schizophrenia is available (77), and an article on this topic appears in this issue of the *Israel Journal of Psychiatry*. A new drug, laropiprant, has been developed that selectively antagonizes the receptor for prostaglandin D_2, a long-chain fatty acid metabolite, and partly prevents the niacin flush (78). It is yet to be determined precisely how niacin triggers prostaglandin D_2 release and how activation of the prostaglandin D_2 receptor induces skin flushing. In view of the relationship between the niacin flush and schizophrenia, it could be of considerable clinical and theoretical interest to determine whether laropiprant exacerbates the symptoms of schizophrenia.

New Ideas in Schizophrenia Research

New ideas are needed in schizophrenia research and therapy, and vitamin therapy for acute schizophrenia should be one of them. Clinical trials of vitamin therapy will have to compete for funding from public grant agencies, and for patient enrollment with large pharmaceutical industry-sponsored trials that provide much-needed money to psychiatric research institutions. In addition to these financial barriers are the well-known practical difficulties of conducting meaningful randomized clinical trials in acute schizophrenia, with the additional problem of interpreting their results, given the possibly diverse etiologies targeted by the vitamin therapies. A strong case

has been made for a pragmatic strategy of small-scale, carefully conceived and objectively documented open clinical trials and case studies which assemble, through enlightened clinical experience, the elements of an effective therapeutic program which would only then be put to the final test of a randomized clinical trial (79, 80). Empirical trials of this kind are ethical, since the nutritional approach is biologically and clinically plausible, and the vitamins that would be used lack the side effects and toxicity of the antipsychotic drugs. If they proved effective, these nutrients could reduce the exposure of young people to prolonged and potentially harmful drug therapy.

Randomized controlled trials are the gold standard in therapeutics, but as was pointed out by the renowned psychopharmacologist, Louis Lasagna, there are valid ways to acquire clinical evidence of a treatment's promise other than the controlled trial. He cited L-DOPA as an example of a drug that well-designed, randomized clinical trials had "proven" to be ineffective in Parkinson's disease (81). Cotzias's landmark paper was an uncontrolled case series (82).

Acknowledgements

This article is based on a presentation at the Sixth International Congress of Neuropsychiatry in Sydney, Australia, September 12, 2006

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