REVIEW ARTICLE

Vitamins in schizophrenia: a literature review

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ABSTRACT

Background: A number of hypotheses and theories about schizophrenia have tried to explain the disease in various dimensions. Past scientific research demonstrated the relevance of nutrients in mental health. Neurodevelopmental and transmethylation theories suggest the role of nutritional factors (vitamins) and genetic factors in the development of the disease. Vitamins and minerals are involved in one or more biochemical pathways and/or physiological actions which influence the function of the human brain. Vitamin deficiencies leading to oxidative damage, methylation deficits, affecting brain developmental mechanisms and neuro-degeneration may explain well some of the symptoms seen in schizophrenia.

Methods: Pubmed and Medline search, Scopus, journal and textbook articles have been accessed for the review of literature on Vitamin deficiencies in Schizophrenia.

Results: Several nutritional epidemiological studies have provided evidence on the role of vitamins in schizophrenia either in the causation of the illness or as an adjunct in the treatment.

Conclusions: This review provides an overview of the role of vitamins in schizophrenia.

INTRODUCTION

Vitamins, food supplements and tonics, are noted to be prescribed widely in general. The role of vitamin supplementation has been described in a few psychiatric case studies. Vitamins and minerals are involved in one or more biochemical pathways and/or physiological actions which influence the function of the human brain. Vitamins play a major role in number of vital functions, acting as cofactors or as coenzyme and catalyze a number of reactions that occur in the body. Most vitamin deficiencies result in psychiatric symptoms in a significant number of people. In people with psychiatric diagnoses, these deficiencies are often associated with more severe symptoms and poorer outcome from conventional treatment.

This article aims to understand the role of vitamins in the aetiology and treatment of schizophrenia. Literature related to deficiencies in vitamins in persons with schizophrenia is reviewed. Descriptions of early evidence of nutritional deficiencies and the risk of schizophrenia are detailed. While most vitamins are seen to have a role in psychiatric disorders, Vitamins B, C, D, and E are known to play a key role in Schizophrenia. The role of Vitamin co prescription with antipsychotic medication in the treatment of schizophrenia is also discussed. Pubmed and Medline searches, journal and textbook articles have been accessed for the review.

Early evidence of the role of nutritional deficiencies in Schizophrenia

Several decades of research has demonstrated the role of dietary nutrients for mental health. Early research observed symptomatology in persons deficient in the B vitamins, and evidence to demonstrate positive improvements in persons, treated with vitamins and other nutrients. The strongest evidence of prenatal starvation, nutritional depletion and schizophrenia emerges from natural calamities, which, although disastrous, provided, a unique opportunity to examine health effects throughout life of starvation during specific periods of gestation. Historically, the first direct test of an association between prenatal starvation and schizophrenia arose as a result of the Dutch Hunger Winter of 1944-1945, one of the tragic events of World War II. A Nazi blockade of occupied Holland in October1944, and an unusually severe winter, which froze the canals used to transport food, resulted in a famine which grew steadily worse, the daily food ration was mainly bread and potatoes and the population was nutritionally depleted. Mortality was more than double, and fertility (reflected in births 9 months later) was less than half that of the previous year. An early neurodevelopmental finding from the Dutch famine studies was an increase in congenital neural defects,
especially neural tube defects including spina bifida and anencephaly, among a birth cohort conceived during the height of the famine. [10, 11] This finding of an effect on neurodevelopment bolstered the plausibility of prenatal famine as a cause of later schizophrenia. The birth cohort with excess central nervous system (CNS) anomalies was examined for an increased risk of schizophrenia. The Dutch psychiatric registry was used to compare psychiatric outcomes in adulthood for exposed (defined by birth in the famine cities during October 15-December 31, 1945; the height of the famine corresponded to the periconceptional period or early gestation for this cohort) and unexposed birth cohorts.

The primary outcome was a diagnosis of narrowly defined schizophrenia by International Classification of Diseases, Eighth/Ninth Revision, criteria (295.1, 2, 3, 6), as categorized in the Dutch National Psychiatric Registry for the years 1970-1992, during which time the subjects were aged 24-48 years. The study found a significant, two-fold increase in the cumulative risk of schizophrenia in the exposed birth cohort. [12, 13] Inspection of the disease risks for successive birth cohorts of 1944-1946 revealed striking peaks in the incidence of schizophrenia, schizoid personality, and congenital neural defects in this same birth cohort. [14] This occurred in the context of an otherwise stable incidence of these disorders among cohorts exposed to famine during other periods of gestation and cohorts who were completely unexposed to famine during pregnancy. A two-fold increased risk of schizoid personality disorder in the same exposed birth cohort, [15] was reported from data were obtained from military induction examinations conducted on all males when they reached age 18. Unlike the schizophrenia result, which was based on the psychiatric registry data, this finding was not limited to treated cases. It provides further evidence of an effect on schizophrenia spectrum disorders (SSDs) from an independent data source.

The relation of prenatal famine to risk of schizophrenia was successfully examined in a cohort in the Wuhu region of Anhui Province, China. In the late 1950s, a massive famine was precipitated in China by the marked social and economic upheaval known as the Great Leap Forward, which involved agricultural collectivization, use of flawed agricultural practices, and diversion of agricultural labour to other purposes, causing 30-40 million deaths. [16]

Based on the Dutch results, the authors examined whether the risk of schizophrenia was increased in the birth cohorts conceived during the height of this famine. Accordingly, the Wuhu birth cohorts of 1960 and 1961 were defined as the exposed group. These cohorts were conceived in the period of most severe famine for this region, as documented in historical records, and as reflected in birth rates for 1960 and 1961 that were less than one-third the average for 1956-1959. The cumulative risk of schizophrenia among the birth cohorts of 1960 and 1961 was compared with that of birth cohorts prior to and subsequent to the famine. The schizophrenia outcomes were obtained from systematic review of the records of the sole psychiatric hospital in the Wuhu region over the period, 1971-2001. The increased risk was approximately two-fold, similar to that of the Dutch famine.

Several confounders have been considered as limitations to the findings of these studies. Brown and Susser (2008), [17] discussed prenatal stress, social class of origin, the inability to tease apart the effects of different types of nutritional deficiencies or of other substances that may have been ingested that might have toxic potential in the Dutch Study. In the Chinese famine study, famine exposure data were not available by month; hence, the precision of the periods of famine could not be as accurately estimated as in the Dutch famine study. However, the pattern of increased risk of schizophrenia by birth year is consistent with an early gestational effect. [18]

Although, interest in nutrients waned, with the introduction on anti psychotic medication in the 1950s, there has been some attention given to either the deficiency of specific vitamins in the aetiology of mental illness, [19] or the therapeutic value of vitamins in the management of mental illness. [20]

**Prenatal and Neonatal deficiency of vitamins and increased risk of Schizophrenia**

The finding of the peak in risk of schizophrenia and schizoid personality disorder with congenital neural defects in the Dutch famine cohort provides evidence to suggest that a neurodevelopmental disruption plays a role in the vulnerability to schizophrenia.

**Folic acid (Vitamin B9)** has been consistently considered for its association with schizophrenia. Based on current knowledge, there are at least 3 pathways by which prenatal folate deficiency could plausibly influence the risk of offspring schizophrenia. [17] Folate deficiency can impede the synthesis and repair of DNA and might thereby increase the risk of de novo. Second, folate deficiency can impede the production of methyl donors and the methylation of DNA and might thereby affect the expression of genes that regulate neurodevelopmental processes. Third, folate deficiency can impede the conversion of homocysteine to methionine and might thereby lead to accumulation of homocysteine with adverse effects on foetal brain development.

Low maternal folate and elevated third-trimester homocysteine levels may be a risk factor for schizophrenia. [20] Elevated third-trimester homocysteine levels may elevate schizophrenia risk through developmental effects on brain structure and function.
and/or through subtle damage to the placental vasculature that compromises oxygen delivery to the foetus.

Epigenetic mechanisms such as methylation of DNA, could lead to abnormal neurodevelopment and may be important in the aetiology of schizophrenia. Maternal dietary folate intake may play a role in determining methylation levels. The MTHFR gene C677T polymorphism influences folate metabolism and intracellular availability of folate metabolites for methylation. In a meta-analysis of MTHFR C677T genotype and schizophrenia risk, Lewis et al. found that TT homozygotes had a significantly increased risk, OR 1.48 (1.18-1.86) supporting the hypothesis that folate status is a determinant of schizophrenia risk. However, there is also reported evidence to the contrary, that hyperhomocysteinemia and methylenetetrahydrofolate reductase C677T and A1289C polymorphisms are not risk factors for schizophrenia.

The role of prenatal Vitamin D deficiency in increasing risk of adult-onset schizophrenia has been investigated over the several decades. Moskovitz, first suggested that the marked seasonal variations in the serum level of vitamin D may be linked to the seasonality of schizophrenia births. In regions with less winter sunlight, low vitamin D levels are frequently reported during winter. Low maternal vitamin D may impact adversely on the developing foetal brain, leaving the affected offspring at increased risk of adult-onset schizophrenia.

Based on the Northern Finnish birth cohort study, a link between the absence of vitamin D supplementation during the first year of life and a significantly increased risk of schizophrenia in men was found. Another study based on Danish case-control study examined vitamin D status in neonatal dried blood spots confirmed that 25-hydroxyvitamin D concentrations showed significant seasonal variation and were significantly lower in the offspring of migrants compared with native-born parents. The study also reported that the risk of schizophrenia was significantly associated with the higher levels of vitamin D.

We were unable to find literature in low levels of other vitamins in the prenatal and neonatal period and its association with schizophrenia.

**Role of Vitamins in patients with Schizophrenia**

**Vitamin B:**

B vitamins are perhaps the most studied in schizophrenia. While the role of folate in prenatal and neonatal periods is well established, B vitamins such as Niacin (Vitamin B3), Pyrodoxin (Vitamin B6) and Cyanocobalamine (Vitamin B12) are seen to be associated with schizophrenia. The three water soluble B-vitamins i.e. B6, B9 and B12 play a major role in the folate cycle acting as co-factors. This cycle involves folate metabolism, the methionine (or homocysteine) cycle, and transmethylation reactions, collectively known as one-carbon metabolism. Deficiencies in these vitamins or defect in the enzymes involved in this cycle can lead to raised homocysteine levels. When homocysteine levels are raised, a lot of cellular and metabolic activities get affected. The homocysteine hypothesis proposes an indirect and longer term effect of the B vitamins on the functioning of the brain. That is, neurocognitive changes may be mediated by cerebrovascular changes, linked to elevated plasma homocysteine concentrations, which are largely attributable to low levels of folate, B12, and B6. Low folate concentrations, raised homocysteine levels have been reported to be associated with negative symptoms of schizophrenia, increased risk of extrapyramidal symptoms and tardive dyskinesia, and cardiometabolic risk.

Vitamin B12 deficiency has a well-established association with a wide variety of neurologic and psychiatric presentations include slowed mentation, delirium, affective disorder, personality change, and acute or chronic psychosis. Vitamin B12 levels in relation to Schizophrenia risk have not been extensively studied. There are mixed reports on levels of Vitamin B12 in schizophrenia. A study by Silver, on 644 bedridden psychotics reported that 78.3% of schizophrenia patients had vitamin B12 deficiency. In another study, cobalamin levels were higher in patients as compared to controls.

Vitamin B3 (Niacin) has been postulated to have therapeutic effects in schizophrenia. Since 1952, Hoffer, proposed, researched, published and expanded on the adrenochrome theory of schizophrenia. According to this theory, the schizophrenic toxin was an oxidized derivative of adrenaline, known as adrenochrome, which is hypothesized to have hallucinogenic properties. Vitamin B3 could help to reduce the quantity of adrenochrome by simply limiting the production of adrenaline. Hoffer et al., and his team have theorized that an additional biochemical property of vitamin B3 which could explain its therapeutic efficacy. Vitamin B3 is a precursor to nicotinamide adenine dinucleotide, which is present in both oxidized (NAD) and reduced (NADH) forms in the body. In the brain, adrenaline loses an electron to become oxidized adrenochrome. If enough NAD and NADH are available then the oxidized adrenaline is reconverted to adrenaline. These back and forth process continues to occur in the presence of vitamin B3 co-enzymes. However, in the absence of sufficient NAD and NADH, oxidized adrenaline loses an electron and becomes adrenochrome. Studies by Hoffer continue
to show the efficacy of vitamin B3 supplementation as adjunct therapy by preventing the formation of adrenochrome. These theories however have had limited acceptance.

There is little literature on the role of Thiamine (Vitamin B1) in relation to Schizophrenia. One hundred and seventy-two successive admissions to a district general hospital psychiatric unit were examined. Routine psychiatric, drug and dietary histories were taken and signs of avitaminosis B specifically noted. Red cell transketolase (for thiamine deficiency), glutathione reductase (for riboflavin deficiency) and aspartate transaminase (for pyridoxine deficiency) were measured. Of the patients, 53 per cent were deficient in at least one vitamin, 12 per cent in more than one (30 per cent in thiamine, 27 per cent in riboflavin and 9 per cent in pyridoxine). Schizophrenics and alcoholics were significantly over-represented in those patients low in thiamine and in more than one vitamin.

**Vitamin C and E**

Vitamin C is important water-soluble antioxidant in human plasma. Literature on vitamin C and schizophrenia pertains to levels in chronic schizophrenia and the therapeutic value of the vitamin. Vitamin E (tocopherol), an antioxidant assists in minimizing the damage caused by cytotoxic free radical over production. In a hospital based study by Suboticanec et al., schizophrenia patients on the same hospital diet as control group subjects had significantly lower levels of fasting plasma vitamin C (p < 0.05) and 6-hr urinary vitamin C excretion after an ascorbic acid load test (p < 0.01). After administration of 70 mg of ascorbic acid for 4 weeks there was no longer any difference in plasma vitamin C levels between schizophrenia subjects and control group subjects, but the urinary vitamin C excretion after the vitamin C loading test remained significantly lower in schizophrenics (p < 0.05). The administration of 1 g ascorbic acid for 4 weeks, in addition to eliminating differences in the plasma vitamin C level, also increased the urinary vitamin C excretion of schizophrenia patients to the level of the control group subjects. The results of this study are in agreement with the hypothesis that schizophrenia patients require higher levels of vitamin C than the suggested optimal ascorbic acid requirement for healthy humans.

A prospective, double-blind, placebo-controlled, non-crossover, 8-week study, Dakhale et al., showed that oral supplementation of vitamin C with atypical antipsychotic reverses ascorbic acid levels, reduces oxidative stress, and improves psychopathology as measured by Brief Psychiatry Rating Scale (BPRS) score. The patients with schizophrenia were divided randomly into placebo and vitamin C group of 20 each. Serum MDA (malonaldehyde), an indicator of oxidative stress and plasma ascorbic acid were estimated by methods of Nischal and Aye, respectively. Increased serum MDA and decreased plasma ascorbic acid levels were found in schizophrenic patients. These levels were reversed significantly after treatment with vitamin C along with atypical antipsychotics compared to placebo with atypical antipsychotics. BPRS change scores at 8 weeks improved statistically significant with vitamin C as compared to placebo. These studies indicate that vitamin C supplementation improves the clinical symptoms and reduces the free-radical induced damage in patients.

Vitamin E has been proposed as a treatment for neuroleptic-induced TD. Vitamin E prevents or decreases the severity of TD particularly in those who had the onset of the problem in the preceding five years. A review of 11 controlled, therapeutic trials with vitamin E found that all but except 2 of the trials showed efficacy for vitamin E, either in the full samples or in the subgroup with TD for not more than 5 years, using the change from baseline in the total score (sum of items 1 to 7) for the Abnormal Involuntary Movements Scale (AIMS) as the measure of reduction in abnormal movements. However, each of these studies was a single-site trial, had a relatively small sample (from 8 to 37 subjects), took place before the introduction of atypical antipsychotic medications, and except for one trial by Adler, most were over short treatment duration.

A study by D’Sousa, found depleted antioxidant levels in Schizophrenic patients when compared to normal subjects as evident from decreased levels of vitamins E and C in the plasma. The same group of subjects were more susceptible than control subjects to oxidative damage as evident from increased MDA levels in plasma. Impaired antioxidant defence and increased lipid per oxidation suggests that treatment with antioxidants (Vitamin E, Vitamin C, beta carotene) at the initial stages of illness may prevent further oxidative injury and deterioration of associated neurological deficits in Schizophrenia.

**Therapy augmentation with vitamins and minerals**

Research in the value of vitamins in schizophrenia has been discussed along two lines. One, based on the findings of the famine studies, the potential implications of prenatal nutrition to prevent schizophrenia have been elucidated. Although data on preventative nutritional strategies is sparse, the authors argue that the merits of nutritional supplementation and food fortification campaigns in the prevention of other disorders should inspire prospective studies of prenatal nutrients in schizophrenia. They recommend neonatal cognitive outcomes be included in randomized control trials of various prenatal nutritional interventions follow up these cohorts for later mental illness outcomes.
A number of past and recent studies continue to show the efficacy of vitamin supplementation in the treatment of schizophrenia.

A double blind placebo controlled crossover study by Lerner et al. [44] reported high doses of pyridoxine (400 mg/day) to be effective in reducing symptoms of tardive dyskinesia in patients with schizophrenia. [45,46] In the study for 4 weeks at a time, split by a one week washout period. Pyridoxine treatment resulted in improvements in both the dyskinetic movement and Parkinsonian subscales with return to baseline when pyridoxine was withdrawn. [4] Several studies have reported success with Niacin therapy. [44] However, these conclusions have been criticized for failure of the investigators to support their claims with evidence from double-blind and placebo-controlled studies, which are necessary to ascertain the efficacy of vitamin treatment of schizophrenia. Riboflavin, Folate, pyridoxine and cobalamin have been recommended by many studies to reduce homocysteine accumulation in schizophrenia.

**DISCUSSION:**

Although sporadic through time, there is growing epidemiological evidence on the role of nutritional deficiency and schizophrenia. Literature demonstrates that vitamin deficiencies play a vital role in prenatal period as a proposed etiological factor. The role of elevated homocysteine as a risk factor for adult schizophrenia has been well documented in a number of studies. However, replication of these findings in larger samples would be needed. The series of research on Vitamin D has hypothesized that increased risk of schizophrenia was significantly associated with lower concentrations of the vitamin in the prenatal period. The single unexpected finding of increased risk of schizophrenia with the highest levels of Vitamin D needs replication to be of etiological significance. The role of Vitamin D hypovitaminosis in childhood and in puberty can also cause brain damage and needs to be investigated. Folic acid and/or Vitamin D supplements during pregnancy need to be evaluated. However, randomised control trials would pose a methodological challenge, considering the the long gap between exposure and outcome. Vitamin deficiencies after the onset of illness have been linked to negative symptoms of schizophrenia, increased risk of extrapyramidal symptoms and tardive dyskinesia and cardiometabolic risk. However, studies are few and speculative.

**CONCLUSION:**

Key vitamins implicated include Vitamins B3, B6, B9 and B12, Vitamin D, C and E. These vitamins have been implicated in increased risk of schizophrenia or in neurocognitive features seen in schizophrenia, either together or independently. The role of adjunctive prescriptions of vitamins have been studied and recommended. Although vitamins cannot be considered for complete cure, they can be used as effective co-therapy along with the antipsychotics, thereby reducing further loss of neurons. However, an extensive series of comprehensive placebo-controlled trials is required to show the efficacy of these vitamins for use as co-therapy.

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**References**

6. Cornish S, Mehl-Madrona L. The role of vitamins and minerals in psychiatry. Integrative Medicine Insights 2008:3; 33-42
17. Brown AS, Susser ES. Prenatal Nutritional Deficiency and
Ramachandran and Thirunavakarasu: Vitamins in schizophrenia


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