

A CRITICAL REVIEW ON HYPOTHESIS, PATHOPHYSIOLOGY OF SCHIZOPHRENIA, AND ROLE OF VITAMINS IN ITS MANAGEMENTROSMI JOSE¹, VENKETESWARAMURTHY N^{2*}, SAMBATH KUMAR R³¹Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Komarapalayam – 638 183, Tamil Nadu, India. ²Department of Pharmacy Practice, J.K.K. Nattraja College of Pharmacy, Komarapalayam – 638 183, Tamil Nadu, India. ³Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Komarapalayam – 638 183, Tamil Nadu, India. Email: venkateswaramurthy.n@jjkn.org*Received: 04 December 2017, Revised and Accepted: 25 April 2018***ABSTRACT**

This review describes about the literatures addressing the role of vitamin supplementation in schizophrenia. Evidence is suggesting that vitamin supplementation includes Vitamin A, Vitamin D, Vitamin E, Vitamin B complex, and Vitamin C may be important in treatment. In schizophrenia, patients may have increased level of homocysteine (Hcy), due to the polymorphism in methylenetetrahydrofolate reductase and hypofunction of N-methyl-D-aspartate receptors. The vitamins main effects are reduced the Hcy level and maintain dopamine and serotonin levels. Add-on treatment with high-dose B vitamins including B6, B9, and B12 and also Vitamin D can significantly reduce symptoms of schizophrenia more than standard treatments alone.

Keywords: Schizophrenia, Vitamin B, Vitamin D.

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INTRODUCTION

Schizophrenia is a psychiatric illness, which occurs by disruptions in their thinking, perception, affecting language and also self-sense. It involves psychotic experiences such as auditory hallucinations and delusions and also impairs functioning like daily activities [1]. It causes alterations in the distressed person's thinking, functioning, perception, and behavior [2]. It mostly affects males (early twenties) than females (early thirties) [3]. The interactions among genes, environmental and psychosocial factors are also the factors for schizophrenia [4]. Schizophrenia patients have high level of homocysteine (Hcy) in plasma or even methylenetetrahydrofolate reductase (MTHFR) polymorphisms. Hcy of high level in plasma may lead to neurotoxicity through the Hcy effect on N-methyl-D-aspartate receptors (NMDARs) [5].

In psychiatric disorders, the schizophrenia not a common one and 21 million of peoples were affected worldwide. The mortality rate of patients, with schizophrenic, is 2–2.5 times more than normal population. The symptoms reduced by proper treatment but not cured completely. The therapy goal is to improve the life quality and restore psychosocial functioning [4].

Hypothesis and pathophysiology of schizophrenia

Protein misfolding and their accumulation inside or outside the neurons are the major pathological features in the neurodegenerative diseases [6]. Several hypotheses are available for schizophrenia, which includes genetical, neurodevelopmental, glutamatergic, neurochemical (dopamine), and GABAergic hypothesis.

Genetical hypothesis postulates the development of schizophrenia may due to that specific cluster of genes will undergo addition or potentiation determines the individual genetic vulnerability [7,8]. The genetic polymorphism results in gene expression or function alteration, in which the genetic variants like single-nucleotide polymorphisms have minor impact [9].

Neurodevelopmental hypothesis, the effects during the development of embryonal, and fetal brain can result alteration in biochemical

functioning and defect in neural connectivity, which resulting in emotional, cognitive, and intentional dysfunction [10,11].

Glutamatergic dysfunction, a hypofunction of glutamate in corticostriatal projections results a sensory flooding and psychotic symptoms and changes in dopamine concentration occurs by an opening effect in the thalamocortical loop. The glutamate receptors are of two groups, ionotropic ligand-gated ion channels and metabotropic G protein-coupled receptors [12]. The ionotropic glutamate receptors act as ion channels which bind to glutamate and generating a depolarizing excitatory post-synaptic current. NMDARs are allosteric tetrameric and ligand-gated calcium channels, moderated by ions, and endogenous ligands. It is involved in the signal transduction, which is memory related by magnesium that can induce voltage-dependent block. NMDARs are supposed to cause neuroinflammation and apoptosis by excitotoxicity and subsequent downstream events [13].

N-Acetyl cysteine (NAC), precursor to glutathione (GSH), is deficient in the schizophrenic patients [14] and increases plasma GSH levels [15]. It releases cysteine, which may influences/modulates the glutamatergic system by act as substrate and leads to the decrease in symptoms [16]. A clinical trial conducted in schizophrenic patients shows that the administration of 1000 mg NAC twice daily over 24 weeks along with antipsychotic drugs, has a decrease in negative symptoms, global function, and akathisia [17].

Dopamine hypothesis explains that dopaminergic neurotransmission, especially in brain regions, mesolimbic, and striatal regions, leads to positive symptoms and dopaminergic deficits in prefrontal regions, which are accountable for the negative symptoms. The dopamine D2 receptor density is higher in caudate was linked with poorer response on cognitive functions involving corticostriatal pathways, a genetic risk for schizophrenia [18].

In GABAergic hypothesis, the 67 and 65 kDa isoforms of glutamic acid decarboxylase (GAD) are the key enzymes for the GABA synthesis, which is present in altered levels in postmortem brain of patients with schizophrenia. A decline in GAD67 transcript levels has been found in prefrontal and temporal cortex [19]. Certain studies showed that

schizophrenic patients have greater MTHFR mutations which may lead to higher level of plasma Hcy concentration, which has proposed to be risk factor in the development of schizophrenia [7].

The medicinal plants, rich sources of phytochemicals and other active constituents and vitamins, have a major role in neuroprotection [20].

VITAMINS AND SCHIZOPHRENIA

Vitamin deficiencies which may lead to the development of schizophrenia are as follows:

- Vitamin A
- Vitamin D
- Vitamin E
- Vitamin B complex
- Vitamin C.

VITAMIN A (RETINOID)

Vitamin A known as retinoid cannot be synthesized in the body and generally has role in the gene expression, proliferation, cell differentiation, migration, and death. The Vitamin A derivative, retinoic acid (RA) is a potent teratogenic agent and its deficiency may lead to the occurrence of certain diseases such as schizophrenia, psychosis, abnormalities in craniofacial, limb, digit, heart, and urogenital, and these are changes that will occur in schizophrenia. Hence, Vitamin A is essential in the early stage of embryo development and throughout fetal development, but its role is less known in adult brain [21]. Hydrocephalus, characterized by increased the third or fourth ventricle size and/or decreased in the size [22-24] of the hind or forebrain, is a characteristic pattern of retinoid toxicity. The nuclear receptors for RA and the transport proteins for retinoid metabolites are present in all parts of the brain, and delivery of retinoid is controlled throughout embryonic, fetal, and postnatal development [21].

The schizophrenic phenotype and the disease gene phenotype may arise from disruption of the disease gene function by one of the several mutations. Retinoid are profoundly altered the lysosomal enzymes^[25,26] release and had a role in the regulation of the glucocerebrosidase gene. Retinoid dysregulation of the non-mutated gene might result in an end phenotype, psychosis that resembles the psychosis which caused by mutant gene, but without the requirement of gene mutation. Alteration of neurotransmitters is a classic hallmark of the psychosis, and treatments in schizophrenia reflect neurotransmitters action in the psychotic process [27].

Bao *et al.* [28], conducted a population-based study and found that low Vitamin A level in the second trimester associated with increase in disease by 3-fold and no association during the third trimester. Hence, Vitamin A supplementation is more important in pregnant women to avoid the fetal abnormalities.

VITAMIN D (CALCIFEROL)

Vitamin D (calciferol) is both fat-soluble vitamin and steroid hormone. It is found in fish, eggs, vegetable oils, butter, liver, and in fortified milk [29,30] and synthesized in the epidermis of the skin from 7-dehydrocholesterol, by the ultraviolet B component of sunlight [31] it converted to Vitamin D3 (cholecalciferol). Vitamin D receptors are also present in various zones in the central nervous system (CNS) of the human brain [32-35] and potent inducer for the synthesis of nerve growth factor. Vitamin D is neuroprotective [36], prodifferentiating and antiproliferative agent [37], which have role in many brain processes, and Vitamin D deficiency is manifested by rickets [31] and finally leads to osteomalacia, osteoporotic bone fractures, cancer, autoimmune, infectious, and cardiovascular diseases [38]. Perinatal Vitamin D deficiency is a risk factor for the schizophrenia [39,40], especially in older peoples as they have thin or pigmented skin [41,42]. A meta-analysis shows that the schizophrenic patients may have lower level of Vitamin D than healthy peoples (mean difference 14.77 nmol/l; 5.91 ng mL) [43].

Jan *et al.* [44] found that in therapy-refractory patients should check Vitamin D level routinely. Adequate serum Vitamin D concentration is preventing new episodes or in helping in the treatment of psychotic symptoms [29]. Severe negative and cognitive deficits associated with Vitamin D deficiency [45].

VITAMIN E (TOCOPHEROL)

Tocopherol, an antioxidant which is lipid soluble, used in schizophrenic patients to mimics the antioxidant defense system deficits and oxidative damage [46]. Reduced GSH (reduced forms of GSH) level is found in red blood cells of patients [47] and oxidized (glutathione disulfide) forms of GSH level were reduced in patients who receive Vitamin E therapy [48]. GSH has vital role in cellular protection [49] and its concentration is reduced in cerebrospinal fluid (CSF), prefrontal cortex, and postmortem caudate of schizophrenic patients [16,50-54]. The adjunctive intake of Vitamins C and E in schizophrenia needs care because the high dietary intake will cause prooxidant rather than antioxidant actions [55].

Dorfman-Etrog *et al.* [56] conducted a study to observe the Vitamin E effect with supplemental therapy on acute extrapyramidal symptoms in patients, who undergone therapy with neuroleptic drugs, and they concluded that adjunctive therapy of Vitamin E and neuroleptics may diminish the acute neuroleptic severity, which is induced by parkinsonism (neuroleptic-induced parkinsonism) in schizophrenia patients.

VITAMIN B COMPLEX

Vitamin B complex, water-soluble supplements and they do not present in the body for long, and its major action in schizophrenia is the methyl group donation for the synthesis of proteins, nucleic acids, lipids, hormones, and neurotransmitters, especially Vitamin B9, B6, and B12 [57]. The blood levels with low content of Vitamin B are a relatively consistent finding in schizophrenia patients, but the exact relationship between B vitamin status and risk of cognitive or behavioral disorders is unclear. Vitamin B complex will not interfere with antipsychotics, but on an empty stomach, it will cause nausea, stomach discomfort, and yellowing of the urine, not to worry about these effects [58].

Vitamin B12 (cyanocobalamin)

Among youngest peoples, Vitamin B12 level was 10 times more than elder peoples, which contributes protection of brain by slowing free radicals production and cellular reactions. Free radicles are the DNA damaging chemicals [59]. The Vitamin B12 level may decline with age, mainly the methylcobalamin in human frontal cortex, which has role in the regulation of methylation reactions and gene expression. Vitamin B12 deficiency causes accumulation of dopamine, which may cause the psychosis resistant to antipsychotic therapy, psychosis reversed by Vitamin B12 supplementation by not developing any extrapyramidal side effects. While analyzing the previous surveys, it was found that 6–15% psychiatric patients have low B12 level [60].

High Hcy level has involvement in neurological and psychological disorders like schizophrenia [61,62]. Hcy binds with NMDAR and alters glutamatergic transmission, results in dopaminergic neuron toxicity, which cause neuronal apoptosis and oxidative stress, leads to dysfunction in mitochondria, and affects DNA methylation altering gene expression [60].

The methyl group of methionine is activated by converting it to S-adenosyl methionine (SAM), sole methyl donor CNS by adenosine triphosphate, and ethionine adenosyltransferase. S-adenosyl Hcy, the demethylation product of SAM, is then hydrolyzed to Hcy in a reversible reaction. Vitamin B12-dependent enzyme, methionine synthase is involved in the remethylation of Hcy to methionine in tissues.

Many studies found that the main etiological factor for schizophrenia is deficiency of Vitamin B12 and higher homocysteinemia [61,63,64]. Not only Vitamin B12 deficiency but also Vitamins B6 and B9 can also cause

schizophrenia, and the symptoms can reduce by supplementation of vitamins along with the antipsychotics [65,66].

Vitamin B9 (folic acid/folate)

Folic acid is present in leafy greens and meat, needed vitamin for neuron function. Some cases show that it is important for the dementia and schizophrenia patients for energy regulation [67]. The deficiency of folate alone or in combination with monoamine precursors such as Vitamins B6 and B12 may predispose to depression or aggravate mood disorders if already present [68]. Sensitive measures are total Hcy and Vitamin B12 levels for folate deficiency. There also has a link between folic acid deficiency and impaired metabolism of noradrenaline, dopamine, and serotonin [69].

A double-blind placebo-controlled study by Godfrey *et al.* concluded that the patients have Vitamin B9 deficiency and the symptoms improved by daily folate supplementation [70]. Increase in the low functioning of MTHFR load may be the risk for developing negative symptoms, and in genotype, there is no difference in folate levels [71]. Inverse relationship is present between severity of negative symptom and folate level [72].

Vitamin B6 (pyridoxine)

Pyridoxine is essential in the amino acids processing the building blocks of proteins, some hormones, dopamine, serotonin, and melatonin. Vitamin B6 is more effective in tardive dyskinesia to decrease the symptoms [73]. The 100 mg/day is the tolerable limit for Vitamin B6, which is established by Institute of Medicine for adults. Pyridoxine-P and pyridoxal phosphate are the active cofactor form, which is formed by the phosphorylation of pyridoxine and an oxidized form of pyridoxal by the enzyme pyridoxal kinase in the liver. Pyridoxine, a coenzyme for the synthesis of dopamine, serotonin, GABA, carbohydrate and amino acid metabolism. Hence, B6 deficiency may lead to seizures and mental retardation [74].

Lerner *et al.* [75] conducted a study to examine the relationship between psychotic symptoms in both schizophrenic and schizoaffective patients (DSM-IV criteria) and Vitamin B6 therapy. The patients received Vitamin B6 supplementation, 100 mg/day in the 1st week and then 100 mg increments each week up to 4th week and measure the positive and negative syndrome scale (PANSS). The PANSS scores have shown that no variations in the mental state of patients between test and placebo. However, they also concluded that more population is necessary to determine the effect of Vitamin B6 in schizophrenia. A double-blind, randomized, placebo-controlled crossover study in 42 schizophrenia inpatients with plasma Hcy levels >15 µmol/L and daily administration of folate 2 mg, pyridoxine 25 mg, and 400 µg of Vitamin B12 for 3 months and also 3 months for placebo, they found that the lower level of Hcy causes the schizophrenia and vitamin supplementation can reduce the symptoms [76].

VITAMIN C (ASCORBIC ACID)

The role of ascorbic acid in schizophrenia, not exactly elucidated, and the content is highest in brain and CSF than in other body tissues [77]. Deficiency in ascorbic acid content will cause the increase in brain acetylcholinesterase activity, dopamine levels [78,79], and decrease level of norepinephrine level. Vitamin C has action in serotonin synthesis, by the conversion of tryptophan to 5-hydroxytryptophan and also in the binding of serotonin to its receptors [80]. Serotonin precursors are used in schizophrenia treatment had only a slight effect [81], and they require higher loading doses of ascorbic acid to excrete the substance in normal amounts through urine [82-84]. Ascorbate in high amounts may exert antipsychotic effects by inhibiting dopaminergic activity [85-87].

Vitamin C supplementation with antipsychotics reverses concentration of ascorbic acid, which causes reduction in the oxidative stress and thus increases brief psychiatric rating scale score, hence, in the schizophrenic treatment, both the drugs in combination can be used for the effectiveness [88].

CONCLUSION

Many studies reveal that hyperhomocysteinemia and vitamin deficiencies, especially Vitamin D, Vitamin B12, Vitamin B9, and Vitamin B6 may be the responsible factors for schizophrenia. Antipsychotic medications with high doses may only need for a brief period until patients attain mental stability after that low dose of antipsychotic medications with vitamin supplements will gradually help the patients to be back to normal or near-normal function. It is necessary to conduct more extensive studies to observe the schizophrenia incidence and its relation to genetic, prenatal, and malnutrition.

AUTHOR'S CONTRIBUTION

All authors had contributed equally to the review work.

CONFLICTS OF INTEREST

All authors have none to declare.

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