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Zinc and Psychiatric Disorders: A Review

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Abstract

Zinc is one of the micronutrients involved in emotional, cognitive, and behavioural processes. Zinc deficiency is considered to impact mental well-being, with varying degrees of anxiety and stress, consistent with zinc enzymes having important activity in brain growth and functional behaviour. Zinc is a neurosecretory substance or cofactor and is hugely abundant in particular neuron contingent named zinc-containing neurons' synaptic vesicles. The concentration of zinc in the vesicles is estimated to reach 1mmol / L and is just mildly associated with some endogenous ligand. Zinc comprising neurons is located primarily in the forebrain, where primates have evolved into a dynamic and intricate network of connections that interconnect much of the cerebral corticles and limbic structures. Changes in the homeostasis of zinc can be linked with brain disease and inflammatory activity of the brain. Zinc ion dyshomeostasis can also play a function in the ageing neurons as synapses deteriorate. Hence, a greater understanding of the function of zinc in the central nervous system may enable therapeutic strategies to be established where aberrant metal homeostasis is involved in the pathogenesis of the disease.

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INTRODUCTION

In India, one among every seven people who have a mental disorder, ranging from mild to severe. The proportional contribution of mental disorders to the total disease burden in India almost doubled from 1990 to 2017. Among the mental disorders that manifest predominantly during adulthood, the highest disease burden in India was caused by depressive and anxiety disorders, followed by schizophrenia and bipolar disorder. (Ambad *et al.*, 2020) The identification of several zinc-related health conditions has demonstrated clearly how essential zinc is in human nutrition. Being the most common trace element in the body, it is second to iron. (Carl *et al.*, 2014)

Zinc is a cofactor and structural part with over 300 metalloenzymes. Essential sources in human tissue include carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerase, thymidine kinase carboxypeptidases, and alcohol dehydrogenase. Zinc is an essential part of Polymerase DNA and RNA. It forms zinc fingers and offers many proteins structural stability. Zinc fingers facilitate interactions between DNA-protein and protein-protein which play a crucial role in binding transcription factors and receptors of steroid hormones to DNA to ensure gene expression. Zinc is important in the formation of cytokines in monocytes and T-cells. Hence

it is essential for the proper functioning of the immune system. (Mccall *et al.*, 2000) The nutritional guideline for zinc consumption is 10-15 mg/day for adults and 20 mg/day for pregnant women. Due to decreased phytic acid and fibre in their diets, strict vegetarians can require as much as 50 per cent more zinc each day. Zinc is primarily found in foods often attached to proteins; the bioavailability of dietary zinc relies on the digestion of these proteins also release zinc. It enables it to bind inside the intestinal tract to amino acids, phosphates, peptides, and other ligands. Red meat and seafood are the most available dietary sources of zinc, while white meat and flesh from young animals have less zinc.

Wheat germ and whole bran are healthy sources of zinc, but food processing and milling reduce their zinc content (Meyers *et al.*, 2006). Dietary intakes of zinc in older people are lower due to decreased energy needs. It is not clear whether ageing impacts the adaptive homeostatic system, or how ageing affects the role, expression, or gene regulatory responses to zinc transporters. (Fairweather-Tait *et al.*, 2008) Zinc Dysregulation is correlated with reduced immunological activity, growth retardation, gastrointestinal problems, spectacular. Insufficiency in zinc is often linked with neuropsychiatric symptoms that may pose as impaired actions and memory, decreased cognitive capacity, and depression (Petrilli *et al.*, 2017). Common mental health conditions include mood disturbances, anxiety disorders such as post-traumatic stress disorder (PTSD), panic disorders, eating disorders, concentration deficit disorder / ADD / ADHD, and autism.

Nevertheless, major depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder (OCD) are the four most prevalent psychiatric disorders which trigger disabilities. For many Asian and American countries, the dietary intake trend of the general population reflects that they are sometimes deficient in several nutrients, especially important vitamins, minerals, and omega-3 fatty acids. A notable feature of the diets in patients suffering from mental disorders is the severity of deficiency in these nutrients. Studies have indicated that daily supplements of vital nutrients are often effective in reducing patient's symptoms. (Murray and Lopez, 1996; American Psychiatric Association, 2013)

Mood disorders

1. Major depressive disorders
2. Bipolar disorder
3. Seasonal affective disorders
4. Cyclothymic disorder
5. Premenstrual dysphonic disorder
6. Persistent depressive disorder (dysthymia)
7. Disruptive related to medical illness

Zinc and Depression

Depression is a widespread illness globally, impacting more than 350 million individuals and comprising 4.4 per cent of the world's population. Depression varies from the regular changes of attitude and short-lived emotional reactions to daily difficulties. Mainly if it is long-lasting and of mild to extreme severity, depression may become a significant health problem over time. It may cause the individual affected to suffer tremendously and perform poorly at work, at school, and within the family. Depression at its extreme will escalate to suicide. Per year about 800 000 people die from suicide. Suicide is the second leading cause of death in adolescents aged 15-29 (World Health Organization, 2017). Major depressive disorder (MDD) is a persistent disease, marked by elevated relapse levels and comparatively low recovery rates following success for the anti-depressant treatments accessible. Moreover, it is widely understood that MDD syndrome is correlated with ancillary health threats such as cardiovascular and endocrine comorbidities, psychological effects that continue between episodes, and the "neuroprogression" trend whereby organizational performance can be impaired and subsequent incidents that rise in numbers and frequency (Moylan *et al.*, 2013). Studies on zinc deficiency and depression are summarized and discussed in Table 1.

Zinc and bipolar disorder

Bipolar disorders are a neurological illness with cycles of depression and episodes of increased mania in mood; they are particularly harmful medical conditions and may impact as much as 1 of every 25 individuals. Individuals of depressive illnesses, often though not symptomatic, experience extremely stressful periods, regular recurrences, and severe psychosocial impairments. The disorder has its starting in puberty and also in late childhood (Miklowitz and Scott, 2009).

Suicide is a popular outcome for many patients with serious mental illness, which is both a conventional and deeply individualized act. The most prominent medical illness correlated with suicide is depressive disorder and depression. At least 25 to 50 per cent of bipolar disorder patients try suicide at least once. Throughout outpatient facilities, any decision to address mental disorder will precede a suicidal risk assessment (Jamison, 2000).

Table 1: Studies relating to zinc levels and psychiatric disorders

Author, Year	Model	Subjects	Measures	Results	Study Design
(Ranjbar *et al.*, 2013)	Zinc, Supplementation, Major depression.	Major Depressive patients (n=44)	Serum Zinc concentration	Beck test mean score was decreased significantly in the zinc supplement group at the end of 6 weeks and 12 weeks compared to baseline. Zinc supplements, together with SSRIS antidepressant drug, improves major depressive disorder more effectively in patients with placebo plus antidepressants.	Double-Blind Randomised Clinical Trial.
(Jung *et al.*, 2016)	Zinc	Patients with depressive symptoms (n=1514)	Plasma Zinc concentration was measured by atomic absorption spectrophotometry.	Participants with depressive symptoms had lower energy-adjusted zinc intake and lower plasma zinc levels.	A prospective cohort study.
(Swardfager *et al.*, 2013)	Zinc, Meta-analysis	Depressed subjects. (depressed, n=1643 Control, n=804)	Serum zinc measurement in depressed patients	Depression is associated with a lower concentration of zinc in peripheral blood.	Meta-Analysis.
(Styczeń *et al.*, 2017)	Major Depression, Zinc	Depressed subjects (n=114)	Serum zinc concentration	The zinc concentration in the serum samples of patients in the depressive episode was significantly lower from those obtained in the healthy volunteer's group.	Case-Control Study.

Continued on next page

Table 1 continued

Author, Year	Model	Subjects	Measures	Results	Study Design
(Grønli *et al.*, 2013)	Psychiatric disorders, zinc	Psychogeriatric Patients (N=100)	Zinc concentration, Albumin	Zinc deficiency is quite common among psychogeriatric patients and appears to be more prominent in patients suffering from other psychiatric disorders than depression. Level of Albumin was lower in the patient's group than in the control group.	Case-Control Study.
(Mlyniec *et al.*, 2014)	Zinc deficiency, Depression, Antidepressant	Rodents	Serum copper and serum zinc concentration were measured.	The study supports that zinc deficiency reduced serum zn/cu ratio and chronic treatment increased this reduced value.	Animal Model
(Sunitha *et al.*, 2018)	Zinc, Vitamin B6, Depression	Rodents (n=18)	Forced Swimming Test (FST)	Supplementation of zinc and Vitamin B6 to standard treatment fluoxetine yielded better anti-depressant activity than fluoxetine alone in rats subjected to stress.	Animal Model
(Fard *et al.*, 2017)	Zinc, Magnesium, Post-Partum Depression	Post-partum depression (n=122)	Serum zinc and magnesium	No relationship is seen between depression and zinc levels.	A randomized controlled clinical trial.
(Sawada and Yokoi, 2010)	Zinc supplementation, Mood States.	Women (n=30) Group I (n=15, Multivitamin) Group II (n=15, Multivitamin+Zinc)	POMS, Zinc concentration.	Serum zinc levels were increased in group II. The result suggests that zinc supplementation may be effective in reducing anger and depression.	Double-Blind, Randomized and Placebo-controlled procedure.

Continued on next page

Table 1 continued

Author, Year	Model	Subjects	Measures	Results	Study Design
(Russo, 2011)	Zinc, Copper, Anxiety	Anxiety (n=38) Control (n=16)	Plasma copper and zinc. Measured using inductively-coupled plasma mass spectrometry	Zinc therapy is very much effective in increasing the zinc level in the body.	Case-Control Study.
(Roozbeh *et al.*, 2011)	Zinc, depression, Haemodialysis, end-stage renal diseases.	Patients with ESRD and HD (n=135)	BDI, Plasma Zinc, Albumin, BUN	Zinc deficiency may be the reversible cause which might contribute to the increased rate of depression in HD patients.	
(Joe *et al.*, 2018)	Zinc, copper	Cases (n=150) Controls (n=150)	Serum zinc and copper levels by atomic absorption spectrophotometer.	Serum zinc and copper levels were higher significantly in patients with schizophrenia than in the control group, and there was an alteration of zinc and copper metabolism in schizophrenia.	Case-Control Study.
(Tokdemir *et al.*, 2003)	Blood Zinc and copper levels in criminal and non-criminal Schizophrenic Patients.	n=88 (n=44, patients with schizophrenia and no criminal record) (n=44, schizophrenic patients who committed a crime)	Plasma Zinc and serum Copper.	Plasma zinc values were significantly lower in criminal subjects when compared to non-criminal subjects, while mean serum copper values were significantly higher in criminal subjects then non-criminal subjects.	
(Siwek *et al.*, 2010)	Zinc, Depressive episode in patients with bipolar disorders.	Patients with Bipolar disorders (n=129) Type I Bipolar Disorder (n=69) Type II Bipolar Disorder (n=69)	Serum Zinc	Decreased serum zinc concentration occurs in Bipolar Disorder Type I and Probably in a late stage of BD.	

Continued on next page

Table 1 continued

Author, Year	Model	Subjects	Measures	Results	Study Design
(Mcclain *et al.*, 1992)	Zinc supplementation, eating disorders patients	n=45 case= (n=33, eating disorder Patients) controls=(n=12, healthy controls)	Serum zinc, urinary zinc	Zinc deficiency may act as a sustaining factor for abnormal eating behaviour in individual eating disorders patients.	
(Sowa-Kućma *et al.*, 2013)	Zinc, Magnesium and NMDA Receptor, Suicide.	n=17	Zinc and magnesium by flame atomic absorption spectrometry. NR 2A, NR 2B and PSD-95 protein by western blotting.	Alterations in zinc, magnesium and NMDA receptors complex in the hippocampus are potentially involved in the pathophysiology of suicide-related disorders depression, which may lead to functional NMDA Receptor hyperactivity.	
(El-Bakry *et al.*, 2019)	Zinc, Attention deficit hyperactivity disorders.	n=75	Serum zinc	Zinc deficiency was prevalent among the study population; more than half of the children were below the laboratory reference range for zinc. Most of the children with ADHD has comorbid psychiatric diagnoses.	
(Rafalo-Ulinska *et al.*, 2016)	Zinc transporters protein levels, depressed, suicide victims	n=36	Zinc concentration, NMDA, AMPA, PSD-95, 5-HT1A Receptors.	Alteration in zinc transport proteins associated with the pathophysiology of MDD and Suicide.	

Mitochondrial dysfunction in Bipolar disorder

In bipolar disorder, mitochondrial dysfunction is implied based on the following lines of evidence

1. Abnormal absorption of the brain energy measured by 31 P-magnetic resonance spectroscopy, i.e. decreased intracellular pH, decreased phosphocreatine (PCr) and enhanced PCr response to photic stimulation.

2. Possible role in the transmission of bipolar disorder as maternal inheritance.

3. Rising rates of deletion of 4977-bp of mitochondrial DNA of autopsied brains.

4. Comorbidity of affective conditions of some forms of mitochondrial diseases such as autosomal hereditary persistent, recurrent, progressive ophthalmoplegia, and 3243 mutant mitochondrial diabetes mellitus.

Based on these results, bipolar disorders are correlated with mitochondrial DNA mutations/polymorphisms and noticed that polymorphisms 5178C and 10398A are correlated with bipolar disorder. In comparison, 5186C genotype was associated with lower intracellular pH in the brain. Variation of mitochondrial DNA can play a part in the pathophysiology of bipolar disorder by altering intracellular calcium signalling systems, which is responsible for the pathophysiology of bipolar disorders. (Kato and Kato, 2000).

Gender difference in Bipolar disorders

The bipolar disorder varies from female to man. In women, the development of bipolar disorder appears to start later than males, so women are more prone to experience seasonal mood disruption trends. Women are much more likely than men to undergo a depressive crisis, combined mania, and fast cycling.

A prevalent psychotic condition, bipolar disorder II, is more frequent in women than males. Comorbidity of medical and psychiatric disorders is more common in women than men and harms bipolar disorder recovery. While the nature and clinical symptoms of depressive disorders vary between men and women, there is little indication that gender influences mood stabilizer care reaction.

Females can also be more vulnerable to impaired treatment and counselling. Women's diagnosis during pregnancy and lactation is difficult as the mood stabilizers available present possible danger to the developing child and baby. Bipolar conditions are not prevented nor worsened by birth, and many people need continued treatment throughout the birth.

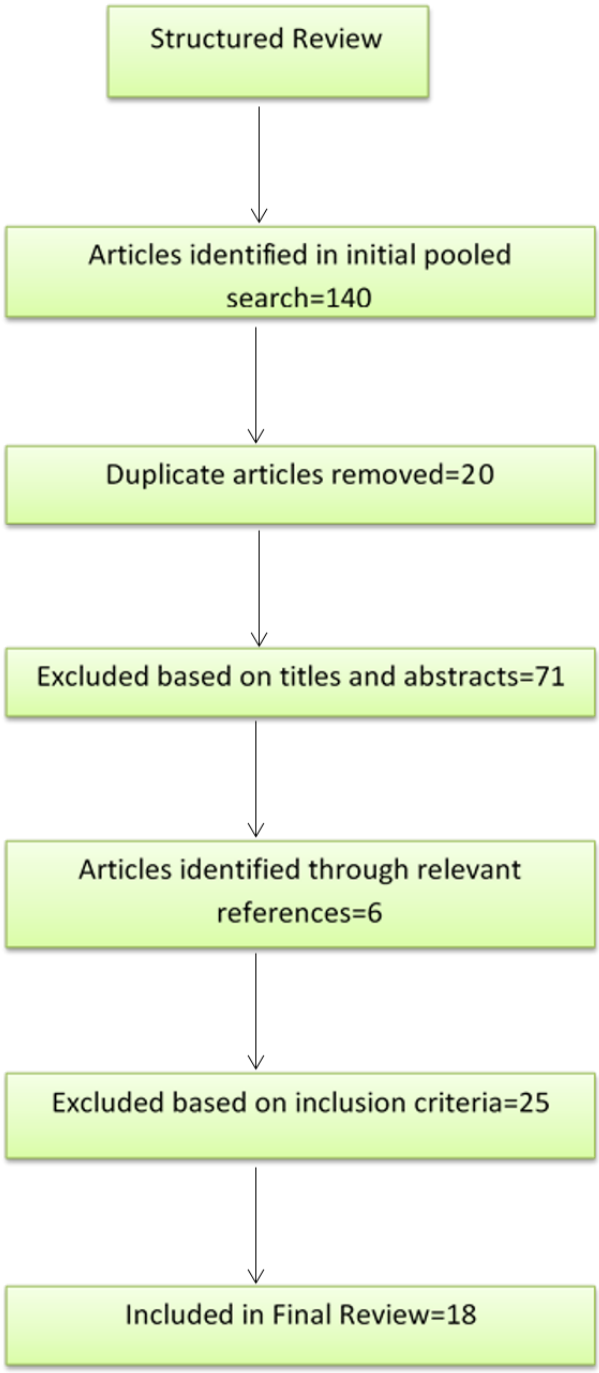

Figure 1: Flowchart of the search strategy and selection process.

The post-partum phase is a time for the development and recurrence of bipolar disorder in women, which could be important for prophylaxis with mood stabilizers. Specific risk/benefit evaluations of pregnant and post-partum women with bipolar disorder are required to support women well-being and to avoid or reduce fetal or baby access to the harmful effects of treatment. (Arnold, 2003)

Study on Zinc deficiency concerning Bipolar Disorders is summarized and discussed in Table 1.

Zinc and Schizophrenia

Schizophrenia is a syndrome: a set of indications and symptoms with unexplained aetiology primarily characterized by researchers as manifestations with psychosis and affected neurodevelopmental and degenerative pathologies involving about 21 million individuals worldwide. (World Health Organization, 2016) In the most extreme type, schizophrenia with psychotic visions and auditory disturbances develops late in puberty early in adulthood. During the last century, these types of diseases improved. The schizophrenic disorder typically develops between the ages of 18 t0 25; some findings suggest symptoms are often sooner apparent. (Insel, 2010) Studies on Zinc deficiency with schizophrenia are summarized and discussed in Table 1.

METHODS

Search Strategy

The review protocol was designed to answer the question "What are the effects of Zinc in Psychiatric Disorders?" We conducted a literature search using MEDLINE electronic database to identify published studies until May 2020. Search terms (Zinc and Psychiatric Disorders). The search was confined to peer-reviewed articles that were published in English and contained an abstract. Reference list of journal articles was also screened for additional citations fitting our search criteria.

Inclusion Criteria

Clinical data on zinc and its association with psychiatric disorders in any global setting.

Exclusion Criteria

1. Review
2. Editorials letters
3. Commentaries
4. Case report
5. Article with unavailable data
6. Psychiatric articles which do not include Zinc or Zinc articles which do not include Psychiatric disorders.

RESULTS

The structured literature search resulted in 140 articles. 20 Duplicate articles were removed, 71 articles were excluded based on titles and abstracts, six articles were identified through relevant reference, 25 articles were excluded based on inclusion criteria, and 18 relevant articles were selected according to the inclusion and exclusion criteria. A detailed summary of the search strategy and result is presented in Figure 1 and Table 1.

NMDA Receptor

The N-Methyl - D-Aspartate (NMDA) receptor is the molecular mechanism for regulating synaptic plasticity and memory function. NMDA Receptor regulation and activity at core synapses may offer hints to clinical approaches for memory loss care. (Cao *et al.*, 2007).

Activation of the NMDAR, a large channel of thrilling ligand-gated ions in the CNS, depends on a few separate events: (a) attachment of the natural ligand (glutamate) and (b) depolarization, which causes the elimination of magnesium ions that otherwise obstruct the ion channel pore.

NMDAR receptor initiates several mechanisms of synaptic plasticity in various brain areas; it is a heterotetramer consisting of two subunits of NR1 and two of four subunits of Nr2: NR2A, NR2B, NR2C and NR2D. The NR2 subunits in the adult hippocampus and cortex are usually NR2A and NR2B, and the ratio of NR2B to NR2A decreases with age in humans and other species, starting before the onset of sexual maturity (Li and Tsien, 2009)

Zinc and NMDA Receptor Activity

A wide variety of extracellular zinc concentrations explicitly and precisely inhibit NMDA receptor responses. In the hippocampus, a strongly enriched area with vesicular zinc, zinc-positive glutamatergic synapses are often enriched with NMDA receptors. (Amico-Ruvio *et al.*, 2011) In many mental disorders, glutamate homeostasis and neurotransmission are dysregulated and severe zinc deficiency that increase the tendency of NMDA receptors. Zinc and other NMDA receptor antagonists displayed therapeutic effects. Another correlation between glutamatergic and serotonergic systems in major depressive disorders is the inflammatory system because zinc rates are decreased by stress and inflammation.

CONCLUSIONS

Zinc is the definitive metal found in our body, and reactive zinc metal is essential for neuronal impulses and is dispersed in large part through presynaptic vesicles. It also plays a large part in synaptic activity. In zinc homeostasis, multiple zinc transporters are involved. Zinc Transporter-3 is a significant transporter of zinc homeostasis in the brain. Alteration of brain zinc status has been shown to have been involved in a wide variety of diseases

such as Alzheimer's disease and mood disorders including depression etc. Zinc may be essential to proper cognitive and emotional activity, and zinc may be a potent neurotoxin. Present review article concludes that zinc deficiency is quite common among psychiatric disorders and review implicates zinc signals in the pathophysiology of neuropsychiatric diseases.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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