Review Article

The Role of Lead and Cadmium in Psychiatry

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Abstract

Psychiatric disorders are associated with long-term disability and huge social and economic costs. The possible influence of heavy metals exposure on public health remains a matter of concern. A recurring research question that persisted among researchers in neuropsychiatry has been "are psychiatric patients more likely to have a high body burden of lead or other heavy metals?" This is an update account on the role of lead and cadmium in psychiatry. This review, which has employed search words like "lead and cadmium in psychiatry" , "lead and cadmium in schizophrenia", "lead and cadmium in psychosis" in citation indices such as PubMed, Google Scholar, Scirus, and Scopus. A total of 415 articles were found; 60 fulfiled the inclusion criteria. Evidence-based information suggests that lead and cadmium may be involved in psychiatry. Should environmental lead and cadmium be implicated in the etiogenesis of psychiatry given the characteristic high environmental pollution in Sub Sahara Africa, it is worthwhile for toxicologists and scientists in Sub-Sahara Africa to investigate if lead and cadmium can become additional biomarkers in the diagnosis of psychiatric disorders.

Keywords: Cadmium, Environmental health, Lead, Psychiatry

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Introduction

Neurological diseases and disorders are rarely unidimensional or unifactorial. Even those diseases, whose etiologies seem closely linked to genetic predispositions, tend to be the product of multiple and intertwined risk factors, of which environmental chemical exposures may serve as one component.[1] Psychiatric conditions including madness, mania, melancholia, and schizophrenia spectrum disorders (SSDs) are mental illnesses of unknown etiology, typically diagnosed in adolescence or adulthood. These diseases, which lack definitive curative modality, are frequently associated with long-term disability and huge social and economic costs. According to Freeman (1984), areas with high population densities are associated with higher rates of criminality, mortality, social isolation, air pollution, and noise.[2] Rates of psychiatric disorders seem to correlate with urbanization. Following the Dohrenwend and Dohrenwend contribution on psychiatric disorders in urban settings,[3] other workers have shown higher overall rates in urban areas and specifically, somewhat higher rates for depression.[4-8] The breeder hypothesis assumes that various environmental factors cause illness. Urbanization is modestly but consistently associated with the prevalence of psychopathology.[9] Dekker *et al*. (2008)[10] confirmed that psychiatric disorders are more common in more urbanized areas in Germany. They opined that the urban-rural differences may be related to environmental risk factors. Van Os *et al*.[11] found a relation between psychotic symptoms and the lifetime prevalence of psychotic disorders, and between psychotic symptoms and urbanization.

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The construct that low level of lead and cadmium exposure can damage the brain and increase the risk of psychiatric disorder — a leading cause of morbidity and disability — is of great concern to overall health. Exposure to lead is widely recognized as a major risk factor for several human diseases, and the structure of industrial ecological systems has made exposure to lead unavoidable for most people alive today.[12] The possible influence of low-level lead and indeed other heavy metals exposure on public health remains

a matter of concern. Over thirty years ago, the research question that persisted among researchers in neuropsychiatry was "are psychiatric patients more likely to have a high body burden of lead or other heavy metals?" Although recent findings suggest involvement of toxic heavy metals in psychiatric illness. Research has shown evidence for this notion; however, the exact underlying factors are not fully understood. This is an updated account on the role of lead and cadmium in psychiatry.

An electronic and manual search of the terms search words like "lead and cadmium in psychiatry", "lead and cadmium in schizophrenia", "lead and cadmium in psychosis" in citation indices like PubMed, Google Scholar, Scirus, and Scopus. Articles were not discriminated by date of publication. Studies also had to be published in English and conducted with human subjects in most cases.

A total of 415 articles were found 60 met the inclusion criteria. Evidence based information suggest that lead and cadmium may be involved in psychiatry. The effects of lead and cadmium in psychiatry are shown on Tables 1 and 2, respectively. Three of these studies namely Stanley and Wakwe,[13] Karim *et al*.,[14] and Arinola *et al*.,[15] inspite of the poor record keeping are from developing nations. Various studies[13-24] using different research designs have implicated increased bone and blood lead levels with different forms of psychiatric conditions ranging from depression, schizophrenia, bipolar disorder, mood disorders, etc. All the studies associated depression, schizophrenia, and bipolar disorder with significant increases in the body burden of lead except Karim *et al*.[14] who noted non-significant increase in serum levels of lead in schizophrenia and suggested further studies. Stanley and Wakwe[13] indicated that lead was increased in depressives ($P < 0.01$) and schizophrenics ($P < 0.05$) but not in manic patients. Eum *et al*.[23] found increased depressive symptom

Table 1: Effect of lead in psychiatry

Authors	Study design	Finding	Ref No
Baker *et al*., 1983	Prospective study of 107 workers exposed to lead in a foundry matched with 65 unexposed workers	Increased rates of depression, among workers with blood levels over 40 mcg/d	16
Maizlish *et al*., 1995	World Health Organisation neurobehavioural core test battery (NCTB) in a cross sectional study.	The frequency of depression significantly increased with increased blood lead level.	17
Stanley and Wakwe, 2002	Twenty-one Depressives, 20 Manic-depressive and 20 Schizophrenics matched with 20 "healthy" individuals were used as controls.	Lead was increased in depressives ($P < 0.01$) and schizophrenics ($P < 0.05$) but not in manic patients.	13
Rhodes *et al*., 2003	Normative Aging Study	Bone lead levels reflect and, could be a risk factor for psychiatric symptoms even at modest levels of exposure.	18
Schwartz *et al*., 2005	Longitudinal study of 803 current and former lead workers	Increased blood lead level in depression	19
Karim *et al*. 2006	Random recruitment of 30 patients and 30 healthy volunteers as control.	Increased serum levels of lead associated with schizophrenia	14
Opler *et al*., 2008	Two hundred and forty-one pooled matched sets of cases and controls from both the California and New England sites using a multilevel random-intercept logistic regression model.	Provided further evidence for the role of early environmental exposure to lead in the development of adult-onset psychiatric disorders.	20
Bouchard *et al*., 2009	Cross-sectional epidemiologic survey. A total of 1987 adults aged 20 to 39 years who responded to the National Health and Nutrition Examination Survey (1999-2004).	Low levels of lead exposure, higher blood lead levels were associated with increased odds of major depression and panic disorders	21
Arinola *et al*., 2010	Twenty healthy volunteers(controls) and 35 schizophrenic patients	Lead was significantly raised in newly diagnosed drug-free schizophrenic patients compared with controls	15
González-Estecha *et al*., 2011	Twenty-five hospitalized patients diagnosed with bipolar disorder matched with 29 healthy controls without psychiatric disorders	Increased blood and urine lead in bipolar disorders	22
Eum *et al*., 2012	Nurses' Health Study (NHS) cohort. 617 Nurses participants	Association of low-level cumulative lead exposure with increased depressive and phobic anxiety symptoms among older women	23
McFarlane *et al*., 2013	Prospective cohort	Associations between early lead exposure and emotional/behavioral functioning in children might persist into adulthood, at least for females.	24

Table 2: Effect of cadmium in psychiatry

Authors	Type of study	Finding	Ref. No
Stanley and Wakwe, 2002	Twenty-one Depressives, 20 Manic-depressive, and 20 Schizophrenics matched with 20 "healthy" individuals were used as controls.	Cadmium was raised in depressives ($P < 0.02$) and reduced in mania patients ($P < 0.01$).	13
Karim *et al*., 2006	Random recruitment of thirty patients and thirty healthy volunteers as control.	Increased serum levels of cadmium associated with schizophrenia	14
Arinola *et al*., 2010	Twenty healthy volunteers(controls) and 35 schizophrenic patients	Cadmium was significantly raised in newly diagnosed drug free schizophrenic patients compared with controls	15
González-Estecha *et al*., 2011	Twenty-five hospitalized patients diagnosed with bipolar disorder matched with 29 healthy controls without psychiatric disorders	Increased blood and urine cadmium in bipolar disorders	22

scores and high phobic anxiety scores in association with increasing bone lead concentration among middle-age and elderly women. The effect of cadmium in psychiatry tended to follow the same trend with the effect of lead.

Hanninen *et al*.[25] found a positive association between lead and depression in agreement with earlier finding among workers with present and past blood lead level <3.4 μmol/l[26] (not shown on the Table). Susser, *et al*.,[27] found association of exhaust plumes and psychiatry decades after pregnant women were exposed to exhaust plumes at a time lead was used in Callifonia.

The public health burden of psychiatric disorders such as depression and anxiety is tremendous — an estimated 450 million people worldwide suffer from psychiatric disorders.[28] Prenatal and neonatal lead and cadmium exposure have been documented to cause common and widespread neurological and psychological effects including depression, anxiety, mood disorders, schizophrenia, etc.[29] Lead, a potent neurotoxin, may affect numerous cell functions, including the release of neurotransmitters such as dopamine and serotonin.

Opler *et al*. in a a study of prenatal lead exposure and schizophrenia using the biomarker of exposure δ-aminolevulinic acid in archived maternal serum samples collected from subjects enrolled in the Childhood Health and Development Study (1959-1966) based in California, suggested a possible association between prenatal lead exposure and the development of schizophrenia in later life. Although there were limitations that hampered an outright conclusion in a follow-up investigation in 2008 by the same team, the results provided further evidence for the role of early environmental exposures in the development of adult-onset psychiatric disorders.[20]

Karim *et al*.[14] reported increased levels of serum cadmium in schizophrenia disordered patients. In the brain lead and cadmium cause lesions including decrease in total cortical volume, white matter,[30] enlargement of cerebroventricular system, changes in gray and white matter and abnormal laminar organization. Various biochemical factors make humans susceptible to neuropsychiatric diseases caused by exposures to a variety of toxic chemicals.[31] It has been postulated that exposure to environmental contaminants may play a role in the development of psychiatric disorder.[32]

The Human Brain and Metallotoxicology

The human brain is susceptible to a variety of toxic chemicals because of natural selection that favors brain structures promoting advanced brain functions such as long-term memory and rapid learning. The high fat content of brain also predisposes it to long-term storage of the same fat soluble toxic chemicals that accumulate in adipose tissue. The high rate of metabolism and high content of polyunsaturated fatty acids also makes it much more susceptible to free radical damage mediated by toxic chemicals, leading to increased damage to brain macromolecules like deoxyribonucleic acid, ribonucleic acid, proteins, cell organelles, and small molecules. The sulfur amino acids are also highest in these brains, making them exquisitely susceptible to exposure to heavy metals. All of these biochemical factors make humans extremely susceptible to neuropsychiatric diseases caused by exposures to a variety of toxic chemicals.[31]

Lead and cadmium in oxidative stress and psychiatry

The mechanism of lead- and cadmium-induced neurotoxicity that lead to neuropsychiatric disorder is not fully understood even in animal studies. However, one developmental hypothesis has it that environmental factors induce pathological changes in the brain before it reaches adult state.[33,34] The pathophysiology of neuropsychiatric disorder is poorly understood, although there is a notion that structural changes occur in the brain of patients with neuropsychiatric disorder. In the brain, lead and cadmium cause lesions including decrease in total cortical volume, white matter[30], enlargement of cerebroventricular system, changes in gray and white matter, and abnormal laminar organization.

González-Estecha *et al*.[22] finding of increased blood and urine levels of lead and cadmium in bipolar disorder may reflect a high past lead exposure in childhood and adolescence. These increased blood lead levels also indicate that oxidative stress may play a role in the pathophysiology of bipolar disorder, as suggested by a meta-analysis showing that oxidative stress markers are increased in bipolar disorder[35]. In the NHANES 1999-2004 study, persons with blood lead levels in the highest quintile (≥2.1 μg/dL) had a 2.3-fold increased risk of meeting DSM-IV criteria for major depression disorder and a 4.9-fold increased risk of panic disorder as those in the lowest quintile (0.7 μg/dL)[21].

The most likely mechanism of lead could be explained, at least in part, by some in vivo studies that suggest that lead exposure causes generation of reactive oxygen species and alteration of antioxidant defense systems[36]. Lead and cadmium have a high affinity for sulfhydryl groups[37]. Some antioxidants, such as N-Acetyl Cysteine (NAC) chelate lead and remove it from the bloodstream[38]. Reducing blood lead levels in bipolar disorder may contribute to an improvement in symptoms in bipolar disorder.

As for cadmium, González-Estecha *et al*.[22] observed a statistically significant increase in the bipolar group with respect to the control group. González-Estecha *et al*.[22] observed an increase in blood cadmium levels in manic phase patients compared to depressive phase patients. An association of lead and cadmium with homocysteine was observed in the NHANES 1999-2002 study as well as in other studies.[39,40] While lead and cadmium may affect homocysteine levels, it is also possible that homocysteine affects blood lead or cadmium levels.[39,40]

Lead and cadmium in mitochondrial dysfunction and psychiatric disorders

In patients with mitochondrial diseases, psychiatric symptoms have been reported. Fattal *et al*.[41] recorded 19 cases of mitochondrial diseases with comorbid psychiatric problems, including bipolar disorder, major depressive disorder, psychosis, anxiety disorders, and personality changes.

Lead and cadmium disrupt mitochondrial functions through many processes leading to energy metabolism and malfunctions in mitochondrial biochemical cascade, as suggested by several studies on the pathophysiology of bipolar disorder, major depressive disorder, and schizophrenia.[34,41-43] There is a correlation between mitochondrial dysfunction and psychiatric disorders. Evidence include impaired energy metabolism in the brain detected using results of magnetic resonance spectroscopy and electron microscopy, co-morbidity with mitochondrial disease, increased mitochondrial DNA (mtDNA) deletion in the brain, and association with mtDNA mutation/polymorphisims of nuclear-encoded mitochondrial genes.[44] Lead is asociated with significant loss in adult gray matter volume of the prefrontal cotex and the anterior cingulate cortex that control executive function, mood regulation, and decision-making. It is suggested that these atrophic changes may be the basis for cognitive and behavioral impairments associated with lead childhood exposure.

Lead and cadmium in neurochemical and hypothalamic — pituitary — adrenal (HPA) axis

In their study on "Childhood and Adult Socioeconomic Position, Cumulative Lead Levels, and Pessimism in Later Life", Peters *et al*.[45] found no direct correlation between lead and depression, but an indirect correlation was found through lead's association with pessimism. This observation is congruent with other studies that found an association between cumulative low lead level and depression.

The etiologic mechanisms underpinning lead and emotional processing have not been fully elucidated.[46] It is not clear if psychological problems are caused directly by lead-induced brain damage or are secondary to conditions surrounding its effect on cognitive performance.[47] Lead is believed to affect the brain systems that regulate social/emotional functioning.[47] Physiologically, lead may alter the functioning of the hypothalamic-pituitary-adrenal (HPA) axis either directly or indirectly, the latter mediated by inducing alterations in neurochemical function.[48] Lead tends to interfere with the release of neurotransmitters by mimicking or inhibiting calcium-mediated processes.[48-51] Lead exposure is of particular interest because it is an established neurotoxin[52] with known effects on several brain systems implicated in depression and anxiety, including monoaminergic signaling[48] and the HPA axis.[48,53] Animal studies have demonstrated that lead exposure affects the hypothalamic-pituitary-adrenal (HPA) axis and can lead to permanent HPA axis dysfunction.[48,54,55] Cory-Slechta and colleagues proposed that alterations in the HPA axis due to lead exposure result in changes in glucocorticoid and catecholamine levels, with neuropsychiatric disorders such as depression as potential consequences.[53] Furthermore, lead affects levels and metabolism of serotonin,[54] and abnormalities in the serotonergic system are present in depression.[56] Lead also affects the mesocorticolimbic system[54], aberrances in which have also been linked to depression.[57,58]

In Nigeria, Lead and cadmium were found to be significantly increased in newly diagnosed drug-free schizophrenic patients compared with controls

according to Arinola *et al*. (2010)[15]. Thus, a mechanism that will decrease blood lead level may be helpful in the management of schizophrenia[15]. González-Estecha *et al*.[22] found high blood lead levels in bipolar patients. It is speculated that reducing blood lead levels in psychiatric patients may contribute to an improvement in symptoms in psychiatric disorders. Hence, the strong association between high blood lead levels seen in aforementioned studies with schizophrenia, bipolar disorder, and mania should be noted and further investigations should be carried out, especially with the suggestion made by the Kanofsky and co-workers[59] that in some susceptible individuals—people predisposed to bipolar illness—a relatively high lead burden can tip their balance towards illness.

Taken together, toxic heavy metals are found in the air we breathe, the food we eat, and the houses we live in. Toxic metal exposure can result in a wide array of common mental health disorders that may mimic many psychiatric "diseases" and thus lead to psychoactive prescription drug use or other unnecessary treatments. Many people are exposed to environmental lead in SSA. Attention should be given by practitioners to correctly diagnose lead-induced disorders manifesting themselves as neuropsychiatric illness. Since studies have shown that many of these complaints tended to be reversed on removal from lead exposure, attention should be given to a patient's work situation and detailed occupational history should be obtained that will identify practices resulting in lead exposure.

Unfortunately, the majority of clinicians dealing with patients who have mental health issues are unlikely to suspect heavy metal toxicity as a cause of their patient's problems due to a general lack of knowledge regarding this subject in the medical community. Unique biochemical, genetic, and nutritional factors can make certain people more susceptible to the effects of toxic heavy metals; thus, each case must be handled on an individual basis.

Although the number of practitioners trained in "functional" or "orthomolecular" medicine is increasing and these practitioners are very familiar with the diagnosis and treatment of problems associated with heavy metal toxicity[60], the case in developing nations is the opposite.

Recommendation

The none recognition of psychiatric disorders and their severity carries an enormous economic and social burden in the developing world especially Sub Saharan Africa SSA where the prevalence rates are feared to be higher than previously thought. Should environmental lead and cadmium be implicated in the etiogenesis of psychiatry given the characteristic high environmental pollution in SSA, it is worthwhile for toxicologists and scientists in SSA to investigate if lead and cadmium can become additional biomarkers in the diagnosis of psychiatric disorders.

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