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Molecular Mechanism of Psychosis

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Abstract:- Biomedical research in line with most baseline studies, has proven biological alterations due to exposure to some heavy metals such as lead, mercury, cadmium, and arsenic have been implicated in patients with neurochemical imbalance, pharmacological viewpoint, and brain imaging as part of psychotic prognosis. Some of the most prevailing psychological conditions with notable tendencies of downheartedness and transience are depression and schizophrenia. However, the basal pathophysiology of these conditions from the pre symptomatic and diagnosed point of view, implicates dopamine, norepinephrine, and 5-HT neurotransmitters. Maternal Immune Activation (MIA) triggered by immunological changes from external factors mutating against the immune cells from predisposition to heavy metals leads to priming of the Central Nervous System (CNS) microglia cells which can create a pathway to expose offspring to psychosis. Based on this information, psychosis has been framed due to deficiency in neural signaling in homeostatic imbalance from oxidative stress, metabolic cascades, influenza, and inflammatory response. This review gives details of the role played by neurotransmitters and heavy metals, their toxicity mechanisms, along with the health effect leading to mental disorders like psychosis, depression, bipolar disorder, schizophrenia etc. Hence, the need for more research in this budding field and the challenges of identifying and developing new treatments for persons predisposed to lengthened risk of neurological autoimmune disorders should be considered.

Keywords;- *Psychosis, Heavy metals, Oxidative stress, Inflammation, Neurology, Neurotransmitters, Schizophrenia.*
Abbreviations; *ROS: Reactive Oxygen Species, GSH: Glutathione, MIA: Maternal Immune Activation.*

I. INTRODUCTION

Psychosis is a medical condition describing someone whose neurotransmitters or brain is not coordinating properly. Some of these manifestations are called hallucinations, delusions, and paranoia [1]. Neurotransmitters act in the capacity of electrochemical signaling molecules and are important for the brain operations. Their dysfunction could result in a lot of mental disorder, therefore, monitoring, and discerning of these substances are quite essential in detecting the functionality of the brain. In the nervous system, neurotransmitters are found in minute concentrations mixed with several other biochemical molecules and minerals, thereby making it difficult to single them out for detection [2].

It is signalized by cognitive deficits (e.g., impaired working memory, distractibility, and impaired executive function), also positive symptoms (e.g., formal thought disorder, abnormal perceptions, and beliefs) and negative symptoms (e.g., lack of motivation, social withdrawal, and anhedonia).

Environmental factors, such as maternal and child health care, immunizations, and environmental pollution (such as exposure to heavy metals), can influence the prevalence of mental disability [3 and 4].

Heavy metal toxicity has been implicated in destroying the functions of the brain, kidney, blood, lungsthrough reduction in their energy levels. Chronic exposure to these metals can cascade into physical, muscular, and neurological deleterious situations that mimic illnesses like Parkinson's disease, Muscular dystrophy, and Alzheimer's disease [5].

Psychosis is believed to be interwoven and diversify in disease conditions that have several pathological sequences coinciding on a clutch of associated prodrome [6]. Onset treatment of the prodromal symptoms of psychosis without delay prevents the prognosis from escalating into deleterious etiology [7]. There are no diagnostic tests for psychosis, it is completely clinical evaluation and there are a lot of psychiatric disorders that present with psychosis e.g., schizophrenia, bipolar mood disorder, delusional disorder etc. A growing framework of literature favors the role of neuroinflammation and oxidative stress in the pathophysiology of psychosis [6]. In this review, projections showing alterations in cellular equilibrium due to oxidative stress and malfunctioning of the immune system due to influenza, neurochemical imbalance and pharmacological effect resulting in divergent growth or trimming of these interneurons leading to psychotic prognosis.

A detailed schematic showing the causes, symptoms, early prognosis importance and signs of psychosis is represented below.

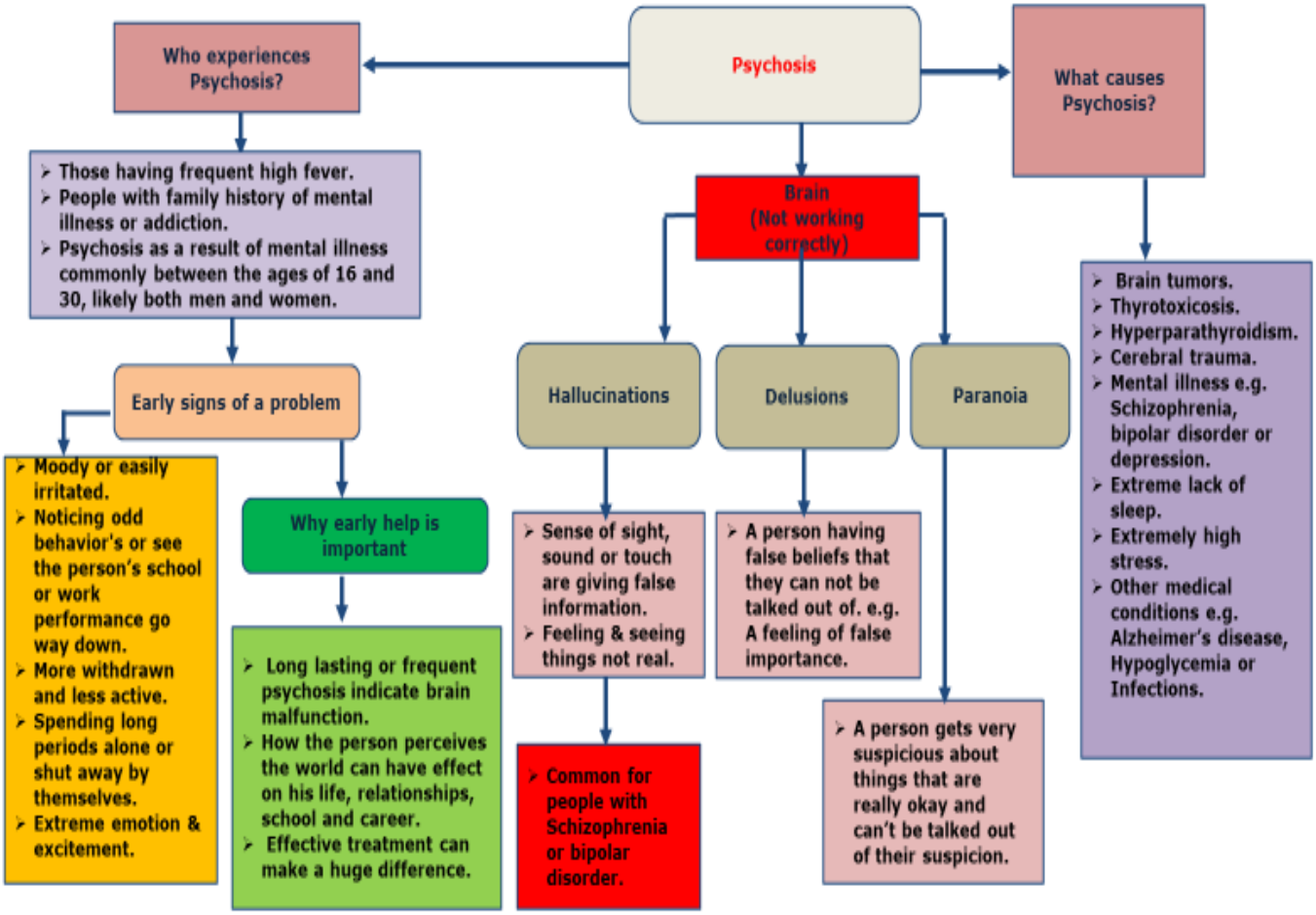


Figure 1.1 *A schematic representation of the pathophysiology of psychotic disorder, causative effect and symptoms.*

II. METHODOLOGY

Several online searches in the databases of Research Gate, PubMed, Springers, European Neuropsychopharmacology, National Institute of Mental Health (NIMH) to mention but a few, were used mostly for the searchusing various terms to arrive at this review. Statistical data and facts sheet were obtained from the web sites of some organizations such as World Health Organization, Centers for Disease Control (CDC) etc. Searched results were critically analyzed, full texts were obtained, inclusion and exclusion standard were applied to obtain appositeness of articles used in this review. Articles were included in whole, parts or extracted form if they lay emphasis on psychosis disorder and mechanism of action. Articles excluded were those of no viable impact to the review and non-English written.

III. RESULTS AND DISCUSSION

3.1 Search Results.

A total of one hundred and thirty-four (134) articles were searched and proposed for use in this review. Afterthorough screening of their abstracts and titles, eighteen (18) articles were expunged, leaving one hundred and sixteen (116) articles to be surveyed. The articles were expunged based on irrelevance; not relevant articles (n=13) thirteen, duplicated copies were (n=3) three, and non-English written were (n=2) two. When reviewed further after putting into perspective inclusion and exclusion standards, eleven (11) more articles were removed leaving a total of one hundred and five articles (105) for this systematic review.

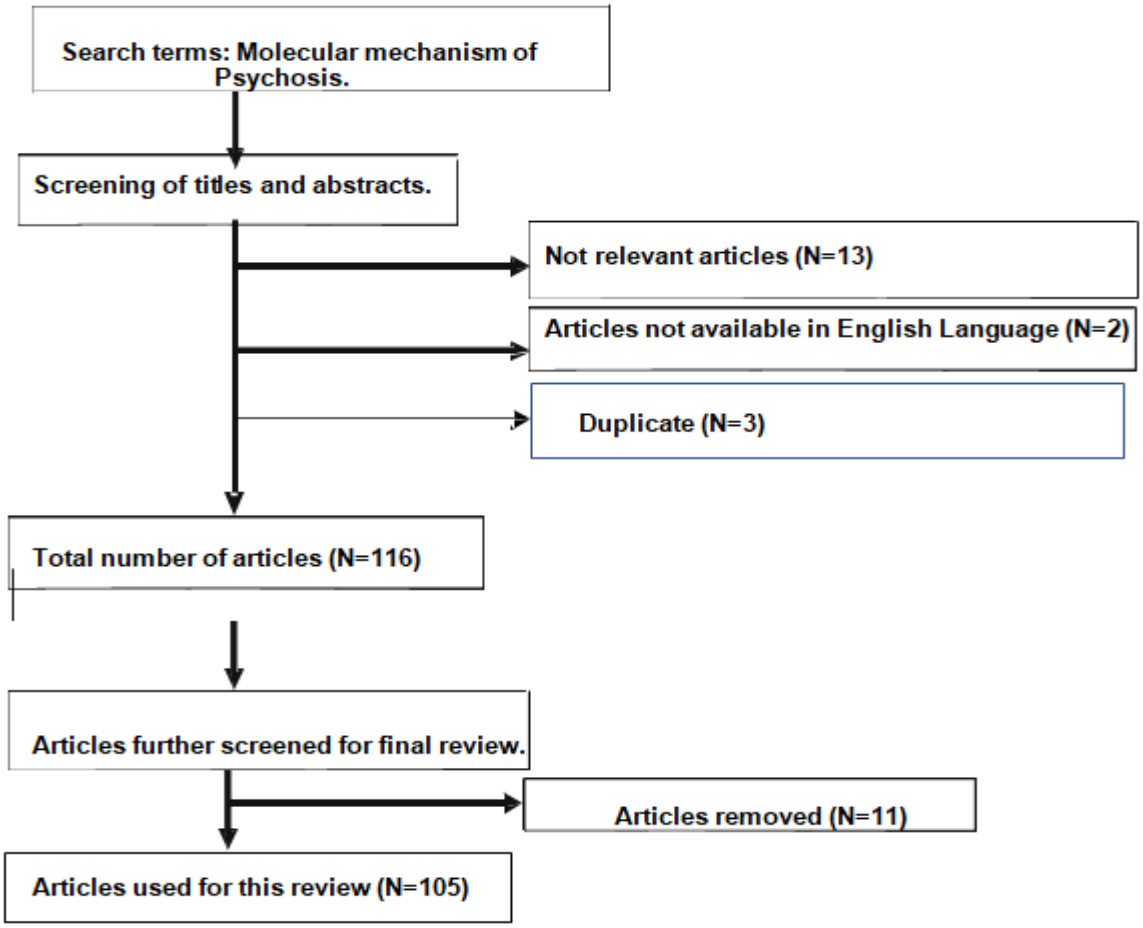


Figure 3.1 ***A search map of the literature review.***

3.2 Neurotransmitters.

Neurotransmitters are chemical messengers that organize the transmission of gestures from one neuron to another through a synapse. They are also a medium through which nerve cells transfer information and relay them round the body. It communicates environmental concerns to the brain by processing this information and generating the right bodily responses suitable for it [8 and 9].

Human emotions, mood, and behavior are greatly influenced by neurotransmission. Throughout the brain and body, you will find receptors that interact with target sites to manage various activities including sleep, appetite, concentration, alertness, pain, mood, cognition, memory, joy, fear, anger, and pleasure [8]. A neurotransmitter must be localized and recognized for accurate monitoring and detection from other biomolecules and other neurotransmitters reasons being that they could have similar characteristics. To qualify as a neurotransmitter, a molecule must measure up to the following: its production and release must be done by the same neuron and kept at the presynaptic end, its emancipation must prompt a particular conduct on the postsynaptic neuron, the exogenous administration must lead to the same effect, and lastly, a specific mechanism can stop its action on the postsynaptic cell [2 and 10].

There are several neurotransmitters found in the body, but the three major ones are dopamine, serotonin, and noradrenaline. They can be easily altered by different personality traits. Dopamine for instance is proven to have played a key role in schizophrenia, a mental disorder, while reduced level of serotonin in the body can lead to poor sleeping pattern and depressed mood [8].

3.2.1 Dopamine.

Dopamine is one of the greatest neurotransmitters for motivational behaviors and motor functions. When acting abnormally, it could result in many psychiatric disorders such as schizophrenia, drug addiction, huntington's disease and parkinson disease [2]. Dopaminergic neurons are found mostly in the subsantia nigra pars compacta and in the ventral tegmental region [11]. It has been established that dopamine plays a key role in drug addiction and is a known fact that cocaine inhibits the transportation of dopamine. More so, cocaine can hinder the reuptake of dopamine by blocking the transportation of serotonin and norepinephrine [12]. Dopamine plays an integra role in cognition and motor neurons. Concentrated cell bodies of the dopaminergic neurons are found in the substantia nigra, the retrorubral field, and the ventral tegmental area projecting to the olfactory bulbs, the limbic regions, basal ganglia, cerebral cortex, and the hippocampus [13]. Rich in dopamine content is the prefrontal cortex which has an exciting role in planning, reasoning, coordination of human performance and problem solving [14].

Newborn with phenylketonuria and likely reduced dopaminergic excitation of the prefrontal cortex, have been diagnosed to have a working memory that is diminished [13 and 15]. In the prefrontal cortex, the catechol-O-methyltransferase (COMT) gene influences the extent to which the dopamine works. The differences in specific cognitive performance in well-developing children are shown to be related in recent times to the genotypic alterations in COMT, bringing about differences in the breakdown of prefrontal dopamine [14 and 16].

Dopamine plays a major role in motivated behavior that is mediated by activating performance conveying internal reward signals [8]. It has been compromised in some psychiatric illnesses such as schizophrenia and disorder in movement control [8 and 17]. Impulsive behavior usually results in a negative outcome because the impulsive individual can cause harm to himself and others. The aspect of dopamine tied to impulsive behavior is the part of the brain system that recompense certain behavioral traits. Such traits include eating food, copulating, a sense of satisfaction or correctness that fortify the involvement in such behavior. These sensational behaviors are mediated by dopamine [8].

3.2.2 Serotonin

Serotonin is a neurotransmitter orchestrated in the brain, necessitated in the activities of the immune, renal, gastrointestinal, and cardiovascular systems. Disruption in the synthesis, uptake or metabolism of the neurotransmitter has been implicated for been responsible for the externalization of depression, compulsive disorder (connected with unwanted and unpleasant thoughts), difficulty in learning and schizophrenia. Serotonin can be secreted as a feedback to several release of stimuli which include mucosal stroking, mechanical distortion, and most notably the release of enteric neurons by electrical stimulation. The motor response in the gut is usually affected by the enteric neurons released by the actions of serotonin [18 and 19]. Serotonin (5-HT) was initially located in the enthero-cromaffin cells and the blood, while presumed to be a vasoconstrictor agent. In the central nervous system in the last two decades, it was discovered that serotonin was considered to stand out as one of the most influential, diffuse, and the most probe neurotransmitters [20].

According to [20], there is notable evidence depicting serotonergic dysfunctions in various psychopathological disorders such as depression, schizophrenia, autism, aggressive behaviors, impulse control disorders etc. Although, several drugs have proven effective therapeutic agents in handling of such conditions such as selective serotonin reuptake inhibitors (SSRIs) which can suppress the symptoms of low or severe depression with little or no side effects as compared to other antidepressants drugs acting on similar capacity.

[20], reviewed that significant stride have been noted not only in using selective serotonin reuptake inhibitors (SSRIs) as therapeutic agent but also in psychosis, there has been advancement of a second-line antipsychotics that focuses on an actual 5-HT receptor isotypes.

Based on studies conducted in literature, there is this impression that 5-HT is a puzzle amongst neuromodulators, meaning it is involved in most things yet not responsible for anything [20and 22]. It was argued that the viable solution to this enigma is by focusing on the individual subtypes of the serotonin receptor. In understanding the functionality of serotonin despite its complexity, is to aim at a selected number of receptor subtypes that have been clearly defined. Looking at it from this angle, you can then start to consider other serotonin subtype [21]. It has been established that the major function of brain serotonin is to improve adaptative response in severe situations through different channels such as a passive channel which enhances the tendencies to be more tolerable towards stress, and the active channel connected to increase plasticity, which when supported, can promote an organism's tendency to align and outweigh stress by modifying its appearance and characteristics. It was also postulated that these two functions are supported by signaling at 5-HT1A and 5-HT2A postsynaptic receptors respectively, while 5-HT1AR signaling has a strong influence under normal circumstances, but 5-HT2AR signaling increases in its function at a critical point in its peak [21].

Due to several information/data published on serotonin, researchers have continued to describe serotonin based on is receptor subtypes, mode of functioning, distribution, and is behavior in both the peripheral and CNS. It's involvement in sleep, sexuality, mood, appetite, aggression, biological rhythms, motor control, memory, vasoconstriction, neuronal degeneration, and gastrointestinal motility [20, 23-26]. A very detailed article showed the role of 5-HT in several disorders that involves neuropsychiatric cases. As established, the dysfunction of serotonin seems to be tied to most psychiatric cases. For example, the treatment of a psychopathological condition with a psychotropic medication can be impeded at first hand by the serotonin process [27 and 28]. Other hypothesis has also proven the role of 5-HT in the pathophysiology of psychiatric disorders.

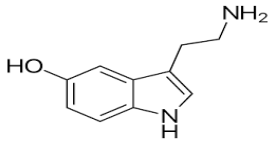
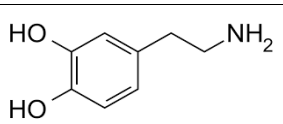
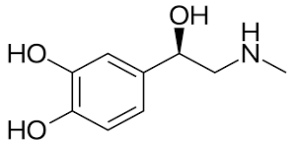
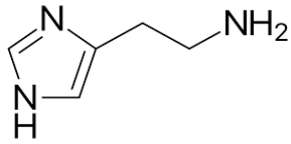
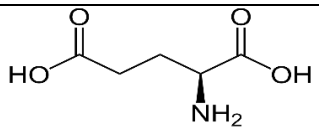
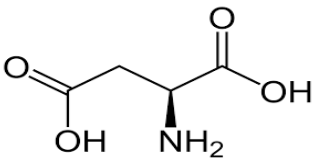
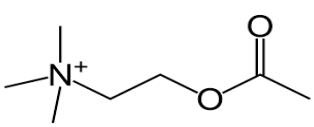
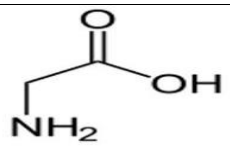
3.2.3 Noradrenaline.

In the cell bodies of the locus coeruleus you will find noradrenergic pathways in the brain projecting to several areas of the spinal cord and cerebral regions. The neurons of norepinephrine projects toward the frontal cortex, and they act close to the limbic system comprising of the hypothalamus, amygdala, hippocampus involved in cognition and emotions. They also play key roles in depressed patient such as their response to pain, pleasure, level of aggression, and appetite [29 and 30]. Report gotten from imaging studies shows that major depressive symptomsrelate to irregular metabolism in the limbic and paralimbic formations of the prefrontal layer. In the amygdala and prefrontal layer of patients with symptoms of constant antidepressant reactions, the irregularity experienced during metabolism is normalized [30], and some neuromodulators such as noradrenaline, acetylcholine, and dopamine can spread at a distance far from its emitted

state to activate receptors at a longer range from its end [31-33]. There are three main G-protein receptors in which noradrenaline acts upon, and they include, α-1, α-2, and β-, adrenoceptors. Depending on the area of concentration and action point of noradrenaline, these receptors complexities are most prominent on synaptic transmission and neuronal excitability [31 and 34]. In the lateral wall of the brainstem close to the fourth ventricle, you will find the locus coeruleus which is a small nucleus of cells located in that region, and in humans, the locus coeruleus comprises about 20,000 neurons and majority of the norepinephrine produced in the brain are done by it [35].

In research conducted by '' [36]'', it was stated that the differential role of norepinephrine as compared to other neuromodulators is because most of its noradrenergic neurons found in the brain are concentrated in the locus coeruleus. Which makes it easier for the locus coeruleus blueprint to be evident in most part of the brain, with the potential of creating both synaptic and non-synaptic correspondence.

Table 3.1: Neurotransmitters and their role in the vertebrate brain.

Neurotransmitters	Formula	Area of accumulation	Pathology and role	Authors
Serotonin		Midbrain, hypothalamus, spinal cord, cerebellum	Schizophrenia, anxiety, vascular disorder, hypertension, obsession.	[18]
Dopamine		Substantia nigra of midbrain, hypothalamus.	Schizophrenia, parkinson disease, feeling of excitement, motivation, reward.	[37]
Epinephrine		Hypothalamus, medulla, locus coerulus, brainstem.	Anxiety, fight, or flight system, increase heart rate, reduced alertness, low energy, pupil dilation.	[2 and 38]
Histamine		Central Nervous System, Hypothalamus.	Alzheimer's and schizophrenia, act on G-protein coupled receptors.	[2]
Glutamate		Brain and spinal cord.	Excitotoxicity, epilepsy, schizophrenia, memory, vision, learning.	[39 and 40]
L-aspartate		Hippocampus	N-methyl-D-aspartate receptor activator, glutamate co-neurotransmitter.	[41]
Acetylcholine		Cerebral cortex, basal nuclei, neuromuscular junction,	Alzheimer's disease, long term effects cause tetanic muscle spasms.	[42]
Glycine		Retina, spinal cord, brain stem.	Hypertonia, hyperekplexia, voluntary motor control and sensory processing.	[43]

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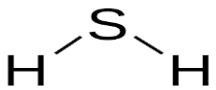
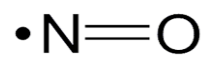
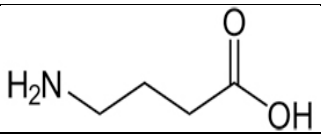
Hydrogen sulfide		Hypothalamus, hypocampus.	Insulin secretion, regulation of vascular tone, myocardial contrition.	[44]
Nitric oxide		Adrenal gland, spinal cord, brain.	Myocardial infarction, factor for relaxing.	[45]
Gamma-Aminobutyric Acid (GABA).		Olfactory bulb, retina, spinal cord, hypothalamus, cerebellum.	Convulsions, epilepsy, excitatory in early development.	

3.3 The Mechanism of Action Implicating Some Heavy Metals In Psychosis.

3.3.1 Mercury.

A major source of mercury includes anthropogenic activities such as agriculture, industrial discharges, mining, and incineration [4 and 46]. Mercury exists mainly in three forms: metallic elements, inorganic salts, and organic compounds, each of which possesses different toxicity and bioavailability. It's uptake by microorganisms gets transformed into methyl mercury within the microorganism, afterwards undergoes biomagnification causing significant disturbance to aquatic lives. Consumption of this contaminated aquatic animal is the major route of human exposure to methyl mercury [47]. Mercury is one of the most toxic elements amongst the studied heavy metals and exposure to high level of this element could permanently damage the brain, kidneys and developing foetus [48-50].

Through diverse mechanisms, mercury can cause biochemical damages to tissues and genes such as disrupting membrane potential, interrupting intracellular calcium homeostasis likewise amino acid pathways in the CNS [51 and 52]. Microtubule destruction, lipid peroxidation, mitochondrial damage [53] and the neurotoxic accumulation of aspartate, glutamate and serotonin are all mechanisms of methylmercury neurotoxicity [52].

With time in the brain, elemental mercury vapor and methylmercury are transformed to inorganic mercury and become tightly wound to sulfhydryl containing macromolecules [53]. Both forms of mercuries also bind to different molecular weight thiol made up of proteins (cysteine, albumin, glutathione etc). The binding of these mercury and thiol complexes are believed to regulate the toxic effects of mercury motility in the body system [54]. The earliest sign of neurotoxicity by methylmercury is the mitochondrial damage from oxidative stress. From research conducted, neural tissue identifies the electron transport chain as the binding site for the generation of free radicals emanating into oxidative damage propelled by methylmercury actions [51 and 52].

Mercury and cadmium have been implicated in generating extremely toxic hydroxyl radicals from the breakdown of hydrogen peroxide which reduces the storage of glutathione [55]. Studies have shown that depletion of glutathione can lead to neurological damage, and reduced presence of glutathione has been seen in Parkinson's disease and cerebral ischemia reperfusion injury [56].

3.3.2 Lead.

Lead targets the memory and learning processes of the brain by inhibiting the N-Methyl-D-Aspartate Receptor (NMDAR), which is essential for hippocampus-mediated learning and memory [57 and 58]. When exposed to Pb, it results to deficits in neurotransmission, while low level chronic exposure to rats have reduced calcium dependent glutamate and γ-aminobutyric acid (GABA) released in the hippocampus [59-61], which shows the dysfunction of presynaptic neuron when exposed to Pb.

Through oxidative stress and ionic mechanism, Pb metal causes toxicity in living cells. From literature, its proven, oxidative stress in living cells is caused by imbalance between production of free radicals and generation of antioxidants to detoxify the reactive intermediates or repair resulting damage [62 and 63]. The figure below shows the attack of heavy metals on a cell through aerobic metabolism and the reaction between ROS production with successive defence shown by antioxidants. Glutathione an antioxidant present in the cell, protects it from free radicals such as H_2O_2. In the presence of increased lead concentration, the ROS increases thereby decreasing the level of antioxidant in the cell. At this stage, neurotoxicity starts occurring through oxidation by macromolecules e.g., DNA, Proteins, Lipids etc, and with time, leading to alterations seen in psychosis.

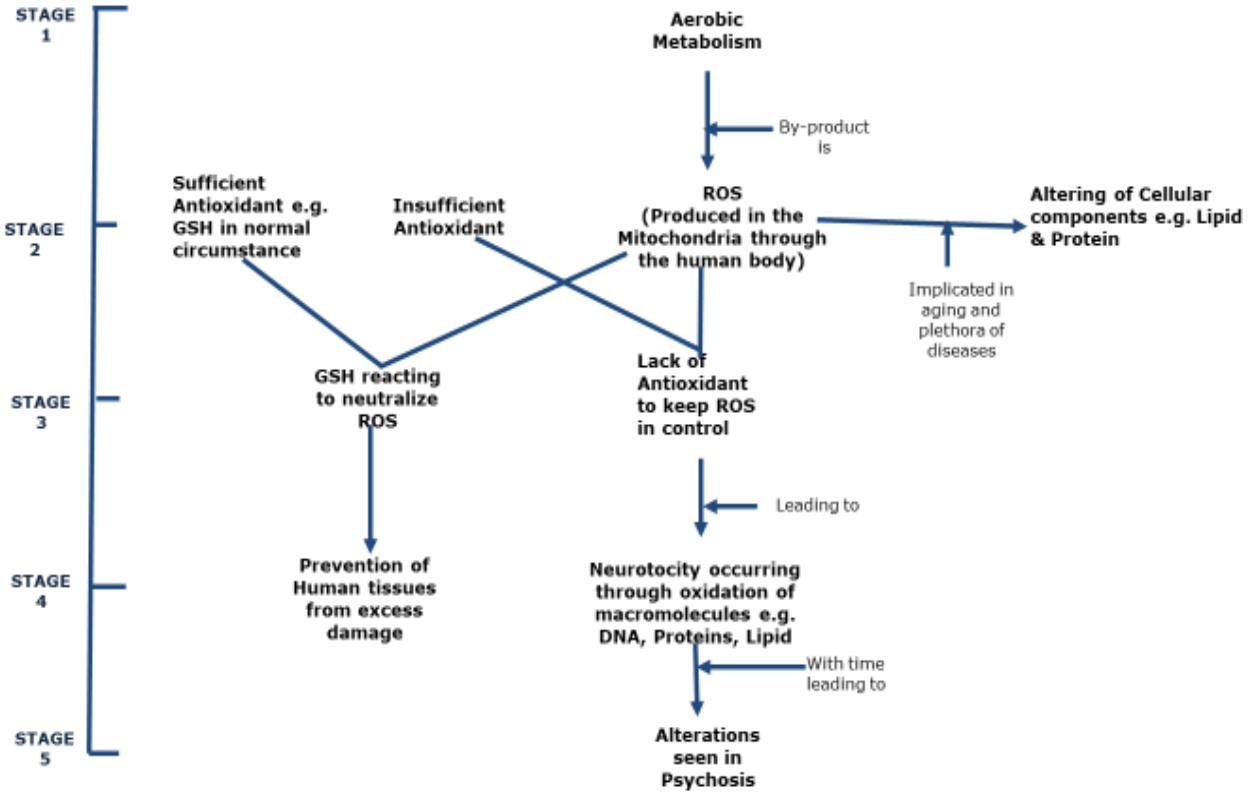


Figure 3.3. The mechanism of action showing the protective effect of antioxidant against heavy metal induced ROS and the aftermath in psychosis.

3.3.3 Cadmium.

Humans can get exposed to cadmium mostly through inhalation and ingestion and could suffer from acute and chronic intoxications as well. Cadmium circulating in the environment is retained in the soil and sediments for prolonged period [5]. Cadmium and lead cause lesions in the brain, as well as decrease in total cortical volume, white matter, abnormal laminar organization, alterations in the grey and white matter and enlargement of cerebra ventricular system [64 and 65].

It is a highly toxic nonessential heavy metal to the kidney, and it accumulates in the proximal tubular cells in larger concentrations. Bone mineralization can be caused by cadmium through renal dysfunction or by bone damage. It is well known for is adverse influence on the enzymatic systems of the cell, oxidative stress and inducing nutritional deficiency in plants. The mechanisms of arsenic- and cadmium-induced damage include the production of free radicals that alter mitochondrial activity and genetic information [51].

Cadmium has the ability to bind with glutamate, cysteine, aspartate ligands and histidine and can result in iron deficiency [66]. It has similar oxidation state with zinc, therefore it can easily replace zinc present in metallothionein, by preventing it from being a free radical scavenger within the cell.

3.3.4 Arsenic.

Humans get in contact with arsenic through natural means, from unintended sources or industrial sources. Water for drinking may get contaminated by inappropriate disposal of arsenical chemicals, use of arsenical pesticides, and by natural mineral deposits. Accidental consumption of arsenic by children or deliberate consumption of arsenic in case of suicidal attempts could be likened to acute poisoning by arsenic [5, 67 and 68].

Arsenicosis; drinking of arsenic contaminated water for a prolonged period, has implications in children's cognitive and psychological development [69]. Those suffering from arsenicosis end up with disease conditions such as cardiovascular, renal, malignancies, neurological and reproductive problem [70]. The most prodromal amongst patients with arsenicosis is skin lesions [71] and is also known for its role in provoking psychological ailment and mental health [72].

Arsenic is a precursor to poison since it attacks mostly the sulfhydryl group of cells resulting to malfunctioning of the cell enzymes, cell respiration and mitosis [5 and 73]

In the biotransformation of arsenic, harmful inorganic arsenic compounds get methylated by fungi, algae, and humans to give monomethylarsonic acid (MMA) and dimethyarsinic acid (DMA). During this biotransformation

process, inorganic arsenic species (iAs) are transformed enzymatically to methylated arsenicals are the arsenic end products metabolites and the biomarker being used for chronic arsenic exposure analysis. The product of biomethylation detoxification process is methylated inorganic arsenic such as MMA and DNA. Although, MMA remains in the cell as an intermediator product, it is not excreted out of the body. As an intermediator product, is found to be extremely toxic compared to others, its responsible for arsenic induced carcinogenesis [74].

Table 3.2: ***Neurotoxicological Effect Due to Exposure to Some Heavy Metals Resulting In Mental Disorders.***

Authors.	Experimental design.	Discoveries.
[64].	An update on the role of lead and cadmium in psychiatry. A total of 415 articles were searched; 60 met the inclusion criteria in this study.	Evidence-based information suggests lead and cadmium may be involved in psychiatry.
[75].	The study design captures two populations chronically exposed to either high (41 children) or low (39 children) levels of arsenic and lead analyzed using Wechsler Intelligence Scale for Children, Revised Version, for Mexico (WISC-RM).	Higher level of urinary arsenic had negative influences on the Central Nervous System function like verbal comprehension, long-term memory, and attention loss.
[73].	Summary of the toxicokinetic and neurotoxicity mechanisms of lead and manganese.	Lead and manganese are metals causing neurological toxicity due to their long-lasting and possibly irreversible nature of their effects. Children exposed to lead come down with cognitive and behavioral deficits.
[69].	This study examines the effect of arsenicosis at school and at home on cognitive achievement of children in rural Bangladesh using current nationally represented school survey data on students. Arsenic exposure was ascertained by the primary source of drinking water tube wells. Population size of n=7,710 (secondary school children; enrolled in grade 8 in Bangladesh).	Cognitive development of the children is significantly negatively affected by arsenic.
[5].	Mechanism and health effect of the true nature of heavy metal toxicity.	Metal toxicity depends upon the absorbed dose, duration of exposure and the route of entering, i.e., acute or chronic. This has led to extreme damage due to oxidative stress induced by the formation of free radicals.
[76].	The implication of mercury, lead, aluminum, copper and some other toxic metals in neurobehavioral functioning and nerve cells was written on this review paper.	At moderate level of exposure to lead and other heavy metals, the young and old are the worst hit by these actions, leading to metal toxicity at the central nervous system. Young children exposed to lead result to permanent loss of IQ ranging from 5 to 7 points, and showing signs of anti-social behaviours and shortened attention span.
[77].	This review paper shows a deep understanding of the mechanisms associated with the elimination of heavy metal toxicity, while identifying substances that played key role in expunging them from living organisms.	The metabolism and excretion of heavy metals from the body depends on the presence of antioxidants such as α-tocopherol, ascorbate, glutathione etc., which are responsible for combating free radicals by withholding the activities of enzymes like catalase, superoxide dismutase and peroxidase.
[78].	25 patients diagnosed with bipolar disorder was hospitalized and paired alongside 29 healthy controls without psychiatric disorders.	There was increased level of cadmium in blood and urine of patients with bipolar disorder.

Most of the study from the table above implicated heavy metals in psychiatry, CNS malfunction, bipolar disorder, neurological toxicity, poor cognitive and memory loss, loss of IQ, shortened attention span and anti-social behaviour. [77] Disclosed that the excretion and metabolism of heavy metals from the body depends largely on the presence of antioxidant present in the cell. As we go further in this review, you will clearly see the role of antioxidant in combating heavy metals thereby preventing the prodromal syndrome associated with schizophrenia and psychosis.

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3.*4 Recent Advances in Lead in Psychosis*.

In the human body, the worst heat organ by lead is the brain compared to others. A singular mechanism is not enough to show the effect of lead in the brain. From research conducted, lead has been indicted to have unmediated neurotoxic effect on the brain which in turn has ties with excitotoxicity of the brain, apoptosis, and emission of different neurotransmitters, cerebrovascular endothelial cells, both oligodendritics and astroglial cells [79]. Lead's ability to replace calcium has been expository in most of its toxicity effect [79 and 80]. According to [80], it was stated that lead can interfere with the calcium-dependent emancipation of dopamine, amino acid, and acetylcholine neurotransmitters. It also further disrupts the thyroid axis that emanate to cognitive indebtedness and psychiatric embodiment. Some of the common prognosis of lead intoxication comprises of vision loss, intellectual decline, and behavioural complications. In recent times, it has also been deduced that antisocial behaviours, delinquency, and violence are all part of medical conditions caused by severe exposure to lead metal [81].

The strong electron sharing characteristics of lead enables it form covalent bonds easily. Intermediate of this lead moiety and the sulfhydryl groups of antioxidant enzymes, you will find these covalent bonds. These bonds are good at making these enzymes defenceless against lead targets, thereby rendering them non-functioning. On the flip side, lead makes glutathione (GSH) indolent by combining with its sulfhydryl group, and this procedure emanates into the production of glutathione from cysteine through the γ-glutamyl sequence which will not be capable enough to replace glutathione inflow [82 and 83]. .Also, lead indolent glutathione, glutathione peroxidase, glutathione reductase, δ-ALAD, and glutathione transferase enzymes magnitude [84]. Lead replaces zinc ions which are also a major co-factor for these antioxidant enzymes; it attacks these enzymes by targeting their sulfhydryl groups and rendering them inactive [85].

From a review conducted by [82], it was stated that upon investigation, the cause of ROS on lipid membrane was lipid peroxidation which was referred to as a major biomarker that give rise to oxidative stress and is highly researched. The ROS act by mutating lipid that produce membrane after taking electrons from the cell that destroys the cell membranes. Other than lipid peroxidation, lead also bring about oxidation to haemoglobin which is a precursor of haemolysis that arises in the red blood cells. There is an occurrence of this process due to the inhibition of ALAD that result in the accumulation of urine and ALA substrate in the blood. The concentrated ALA invariably give rise to superoxide radical and hydrogen peroxide which further interrelate with oxyhaemoglobin ensuing the formation of hydroxyl radicals [82 and 86]. More so, the mechanism that occurred earlier with lipid membrane makes the cell highly prone to oxidative stress leading to apoptosis.

3.5 The Role of Maternal Immune Activation (MIA) in Psychosis.

Evidence from epidemiological findings implicates maternal infection as a major risk factor for schizophrenia and autism spectrum disorder. Results from experiments conducted in animal studies demonstrate that maternal immune activation (MIA) only is enough to cause lifelong alterations in behaviours and neuropathology in offspring [87]. MIA in early gestation period as compared to late one, result in foetal brain cytokine responses and changes in behaviour in adult offspring and neuropathology [88 and 89], whether the duration of exposure leads to distinct CNS disorder is still not clearly defined. The developing foetus CNS is influenced by the immune activation within the maternal compartment through inflammatory mediators found in the blood and amniotic fluid of schizophrenia and autistic mothers [90-92, 88].In offspring, injection of a single inflammatory cytokine (interleukin IL-6, -17 or -2) is enough to induce several autistic and schizophrenia behaviours [88, 93 and 94].

The schematic below shows how MIA leads to psychiatric disorders (schizophrenia and psychosis) in offspring. Infections such as maternal influenza could lead to the release of pro-inflammatory cytokines in the mother's bloodstream which eventually gets to the foetus [87, 92 and 93].

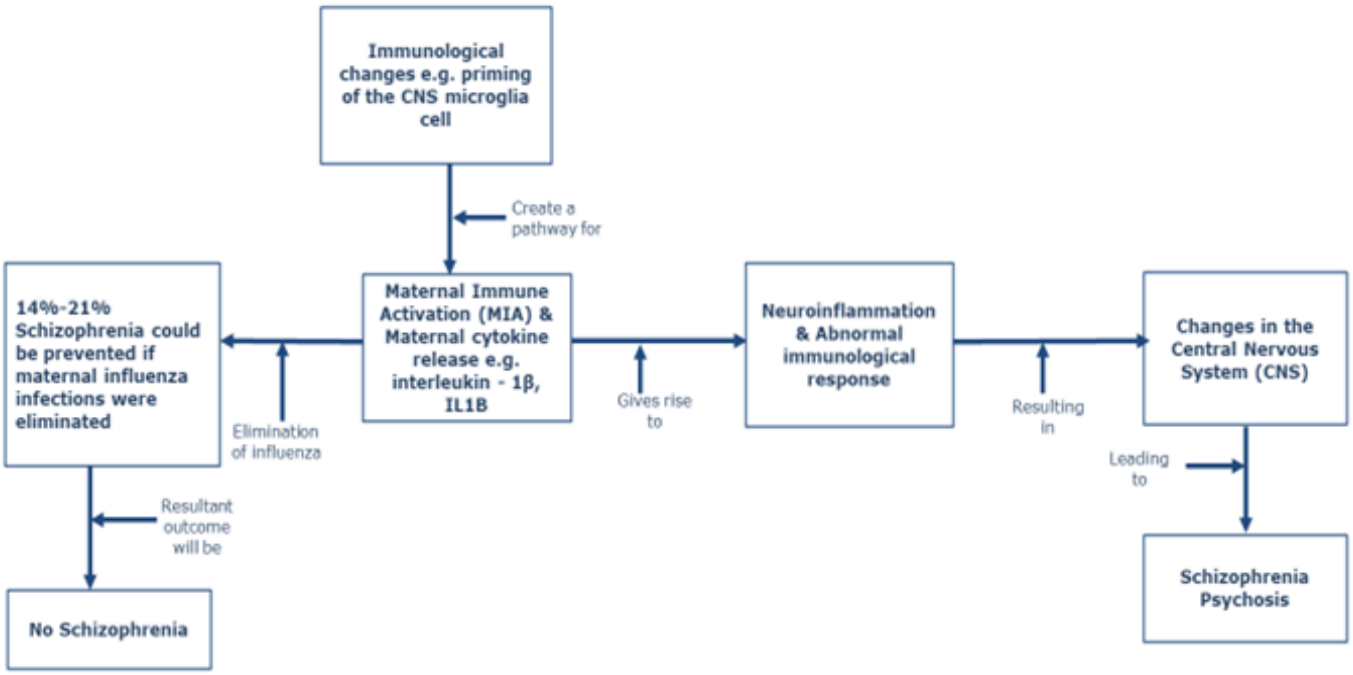

Figure 3.4. A mechanism of action depicting pro-inflammatory cytokines in psychosis.

3.6 Treatment and Management of Psychotic Disorders.

A macrophage-like cell in the brain called minocycline prevents the emergence of MIA-induced behaviours and changes in cytokines in the adult brain when given during exposure to peripubertal stress [91, 95 and 96]. Probiotic treatment can be used to prevent several schizophrenia and autistic related phenotypes in MIA offspring [97]. Anti-cytokine antibody treatment [93 and 98], environmental enrichment [99] or dietary supplementation with zinc [100 and 101], could also be used as similar treatment.

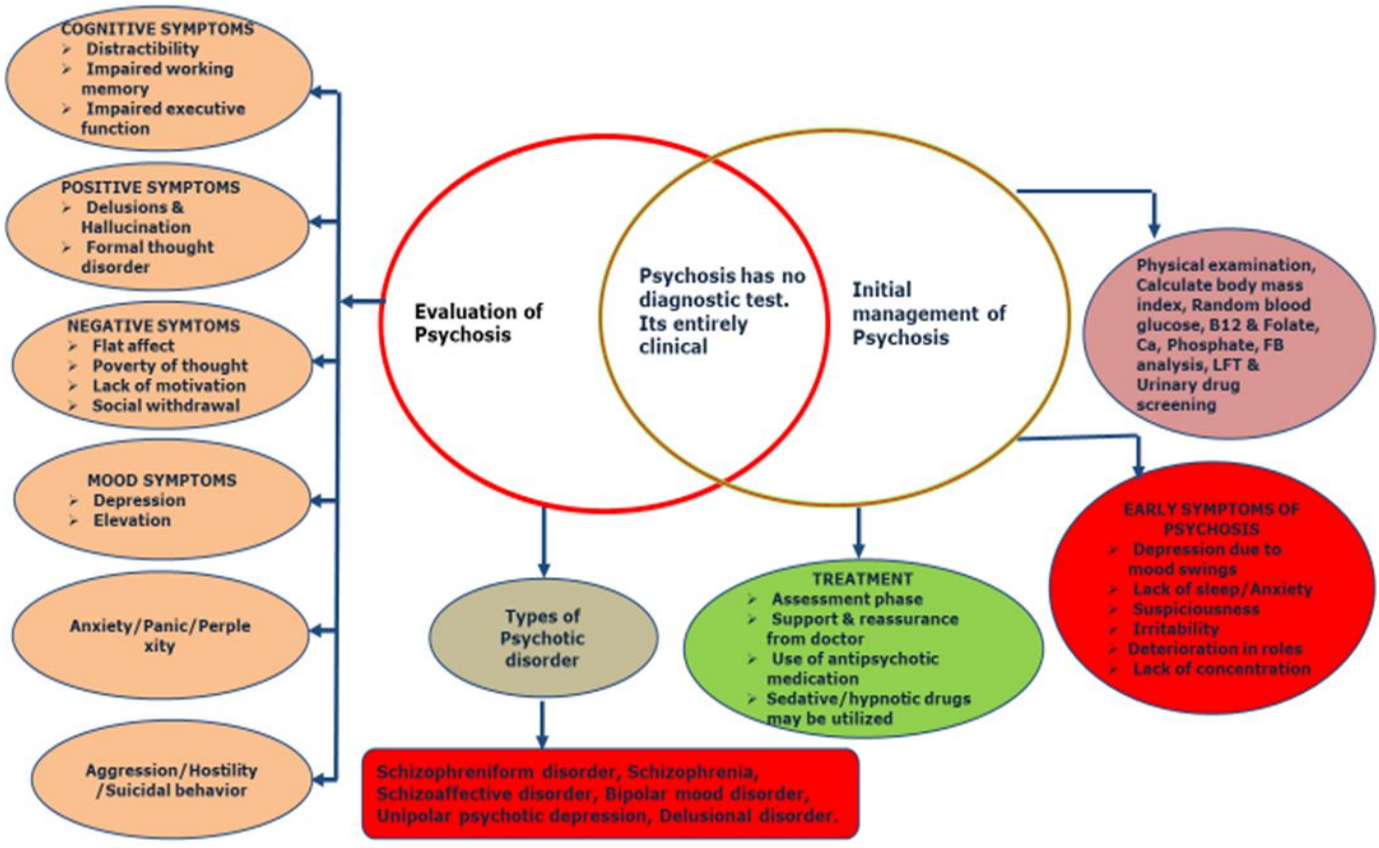

Figure 3.5. A schematic diagram of the evaluation and initial management of psychosis.

IV. CONCLUSION

During prenatal and perinatal stages, abnormal neurodevelopmental processes are seen to begin at that time with Schizophrenia mostly surfacing in the second decade of life [102]. Recently, pharmacological treatment of psychotic disorder acting on the D2 receptors to inhibit dopamine neurotransmission, are either disease modifying than symptom-suppressing [103]. Although, patients in their early stages of sickness initial treatment of schizoaffective disorder or Schizophrenia, reduces progressive decline reoccurrence and duration of psychotic episodes in functional and intellectual endeavors over psychotic disorders throughout the patient's life. For this sole reason, a defined mock-up for the initial stages of psychosis has been build up to improve the clinical benefits of the care [103-105]. While occupational exposure to heavy metals can be tackled through engineering methods, monitoring of the exposure at source or eliminating the use of some raw materials that contains these metallic properties.

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