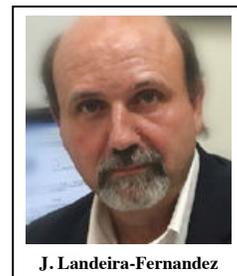


Association of Oxidative Stress with Psychiatric Disorders

Waseem Hassan^{a,b}, Hamsa Noreen^a, Vitor Castro-Gomes^c, Imdadullah Mohammadzai^a, Joao Batista Teixeira da Rocha^b and J. Landeira-Fernandez^{d,*}

^aInstitute of Chemical Sciences, University of Peshawar, Peshawar, Khyber Pakhtunkhwa, Pakistan; ^bDepartamento de Bioquímica e Biologia Molecular, Bioquímica Toxicológica e Programa de Pós-Graduação em Educação em Ciências: Química da Vida e Saúde. Universidade Federal de Santa Maria, Santa Maria, RS, Brazil; ^cDepartamento de Engenharia de Biosistemas; Universidade Federal University de São João del-Rei; São João del-Rei; Brazil; ^dPontifícia Universidade Católica do Rio de Janeiro, Rio de Janeiro, RJ, Brazil



J. Landeira-Fernandez

Abstract: *Background:* When concentrations of both reactive oxygen species and reactive nitrogen species exceed the antioxidative capability of an organism, the cells undergo oxidative impairment. Impairments in membrane integrity and lipid and protein oxidation, protein mutilation, DNA damage, and neuronal dysfunction are some of the fundamental consequences of oxidative stress. *Methods:* The purpose of this work was to review the associations between oxidative stress and psychological disorders. The search terms were the following: “oxidative stress and affective disorders,” “free radicals and neurodegenerative disorders,” “oxidative stress and psychological disorders,” “oxidative stress, free radicals, and psychiatric disorders,” and “association of oxidative stress.” These search terms were used in conjunction with each of the diagnostic categories of the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders* and World Health Organization’s *International Statistical Classification of Diseases and Related Health Problems*. *Results:* Genetic, pharmacological, biochemical, and preclinical therapeutic studies, case reports, and clinical trials were selected to explore the molecular aspects of psychological disorders that are associated with oxidative stress. We identified a broad spectrum of 83 degenerative syndromes and psychiatric disorders that were associated with oxidative stress. *Conclusion:* The multi-dimensional information identified herein supports the role of oxidative stress in various psychiatric disorders. We discuss the results from the perspective of developing novel therapeutic interventions.

Keywords: Oxidative stress, psychological disorders and antioxidant therapy.

REACTIVE OXYGEN SPECIES (ROS)

The development of aerobic metabolic processes causes the generation of reactive oxygen species (ROS) in cellular membrane, endoplasmic reticulum, mitochondria, lysosomes, peroxisomes, cytoplasm and nucleus [1]. Important intracellular sources of ROS comprises peroxisomal enzymes, flavoprotein oxidases and microsomal cytochrome P450 enzymes etc. [2]. A number of environmental features [e.g., ionizing radiation, UV radiation, tobacco smoke, xenobiotics] as well as an initiation of superficial receptors of the cell may also contribute to the augmented generation of ROS [3]. The most devastating and vigorous feature of various ROS is their capability to cause oxidative damage to nucleic acids, proteins, DNA, lipids, cells (cytotoxicity), enzyme inhibition and ultimately leads to cellular death by activating programmed cell death [PCD].

Literature demonstrated that oxidative stress is produced because of the non-homeostatic conditions of oxygen. Approximately 1-3% of the consumed oxygen is converted into ROS. Besides, hydroxyl radical, superoxide radical and hydrogen peroxide are the important ROS. These are the normal metabolic derivatives that are produced through the mitochondria in growing cells [4-6]. ROS can be radicals (e.g. hydroxyl radicals), ions (e.g. superoxide anion) or neutral molecules (eg. hydrogen peroxide). Due to the reactivity of these radicals, ions or molecules, In different species ROS is considered as a cascade of transitions. Classically transfer of one electron to the oxygen results in the formation of superoxide, which changes to hydrogen peroxide in the presence of superoxide dismutase. Superoxide is short-lived and does not readily cross mem-

branes, but superoxide dismutase transformed it to hydrogen peroxide (membrane-diffusible) [12]. Moreover, peroxynitrite (ONOO⁻) is generated by the reaction of superoxide with nitric oxide (NO). The reactions of hydrogen peroxide are catalyzed by peroxidases, which forms the hypochlorous acid (HOCl) and singlet oxygen (1O₂). Finally, superoxide and hydrogen peroxide produces hydroxyl radical uses catalyst (iron ion) by Haber-Weiss reaction [7].

There is a contradiction about the pharmacology of ROS: on one hand, they mediate cell signals and sustain immune system, which are helpful in the prevention of diseases. Conversely, they can destruct important cellular molecules and play a vital part in cardio-vascular diseases [8], carcinogenesis [9], diabetic nephropathy, asthma, arthritis, atherosclerosis, dermatitis, trauma, vasospasms, stroke, hyperoxia, age pigments, liver injury, retinal damage, hepatitis and periodontitis to name a few [10, 11].

Several studies highlighted the physiological importance of ROS in activation and coordination of numerous signal transduction pathways and in immune regulation [12]. ROS contribute in different significant physiological processes e.g. control of inflammatory responses and response to growth factor stimulation [13]. They are also involved in the regulation of different cellular processes like proliferation, apoptosis, contraction, cytoskeletal migration, growth and regulation [14].

REACTIVE NITROGEN SPECIES (RNS)

Reactive nitrogen species (RNS) are a nitrogen containing molecules, derivatives of nitric oxide (NO[•]) and superoxide (O⁻¹), which are generated by the enzymatic activity of nitric oxide synthase 2 (NOS) and NADPH oxidase respectively. RNS are also generated as a result of water and air pollution, certain drugs (e.g., cyclosporine, gentamycin, tacrolimus, bleomycin), heavy or transition metals, cigarette smoke, alcohol, radiation, industrial solvents, cooking (e.g., smoked meat, used oil, fat) and oxygen toxicity. Fur-

*Address correspondence to this author at the Laboratório de Neurociência Comportamental, Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro, Rua Marquês de São Vicente, 225, Rio de Janeiro, RJ, 22453-900, Brazil; Tel: +55-21-3527-2075; Fax: +55-21-35271187; E-mail: landeira@puc-rio.br

thermore, When the formation of reactive nitrogen species in a system exceeds the system's capability to remove and neutralize them else their overproduction causes the nitrosative stress which may lead to the cellular damage and even cell death [15].

Nitrogen dioxide (NO₂•), Nitrous acid (HNO₂), Dinitrogen trioxide (N₂O₃), Peroxynitrite (ONOO⁻), Nitronium anion (NO₂⁺), Nitryl chloride (NO₂Cl), Nitric Oxide (NO•), Dinitrogen tetroxide (N₂O₄), Alkyl peroxynitrites (ROONO) and Nitrosyl cation (NO⁺) are the important RNS that causes the nitrosative stress. Nitric oxide (NO•) is an important reactive nitrogen radical. It is a significant oxidant biological signaling molecule in different physiological processes e.g. defence mechanisms, immune regulation, blood pressure regulation, smooth muscle relaxation and neurotransmission [16, 17]. Peroxynitrite is a nitrating specie and a strong biological oxidant produced from the near-diffusion-limited reaction of the free radicals (superoxide anion and nitric oxide). Literature exposed that because of the reduced availability of nitric oxide, ONOO⁻ leads to the cardiovascular disease (vasorestriction), dysfunctions and cell death. Besides, selenomethionine and selenocystine can be used as antioxidants against ONOO⁻ damage in DNA [18, 19].

ROLE OF METALS

Heavy metals like copper, manganese, iron, zinc, calcium, magnesium, selenium and other trace redox active transition metals are essential in most biological reactions, e.g., in the synthesis of nucleic acid, proteins and as cofactors of various enzymes. Thus their deficiency can lead to disturbances in central nervous system and other organ function [20, 21]. Several studies highlighted the role of metals like cadmium, iron, arsenic, copper, nickel, mercury and lead in the production of reactive oxygen and nitrogen species which causes the carcinogenicity and toxicity in biological systems [22-24]. Metal induced free radicals (•OH) and ion (OH⁻) are generated via Fenton and Haber-Weiss reactions as shown below;

- $M^{(n)} + O^{\bullet-1} \rightarrow M^{(n-1)} + O_2$
- $M^{(n-1)} + H_2O_2 \rightarrow M^{n+} + \bullet OH + OH^-$ (Fenton reaction)
- The overall reaction of the combined steps is called Haber-Weiss reaction.
- $O^{\bullet-1} + H_2O_2 \rightarrow O_2 + \bullet OH + OH^-$
- Metal-mediated generation of free radicals may cause several alterations to DNA bases, lipid peroxidation and changes in sulphhydryl and calcium homeostasis. Furthermore, the metals can induce neurotoxicity, hepatotoxicity and nephrotoxicity [22] [25-27].

CRUCIAL ROLE OF OS/ROS

The biological specificity of ROS is accomplished through localization, duration and amount of ROS formation. ROS have crucial roles in normal physiological processes, such as ion channels, redox regulation of protein phosphorylation, transcription factors, various signaling cascades (i.e., inflammatory responses) [28], cellular processes (e.g. differentiation, proliferation, growth, apoptosis, cytoskeletal regulation, migration, and contraction) [13], immune function, chronic granulomatous disease (CGD), NADPH oxidase NOX2, NOD-like receptor (NLR), thyroid function [29, 30], cognitive function [31] neuronal apoptosis (brain development) [32], neuronal ion channels, kinases, transcription factors [33], NOX enzymes, glutamatergic neurotransmission, ionotropic NMDA receptor (NMDA-R), ketamine, Modulation of nutrient sensors and aging, "target of rapamycin" (TOR), a nutrient-sensing protein kinase and the "AMP-activated kinase" (AMPK). Moreover, ROS also exhibited an important role in bacterial, fungal, and microbial killing [34].

ASSOCIATION OF OXIDATIVE STRESS WITH PSYCHOLOGICAL DISORDERS

Oxidative stress is caused by an imbalance between the production of reactive species (both oxygen and nitrogen) and antioxidant defense system. Vitamin E (tocopherols), C (ascorbic acid), A (retinol), polyphenols and flavonoids are non-enzymatic antioxidants, while enzymatic antioxidants includes, but not limited to sulfiredoxin, superoxide dismutase, aldehyde dehydrogenases, catalase and glutathione peroxidase. Furthermore, free radicals e.g. nitrogen reactive species and reactive oxygen species causes DNA damage, other redox alterations (e.g., ceruloplasm alterations and selenium depletion) and lipid and protein oxidation [35, 36]. Free radical induced oxidative stress leads to various degenerative syndromes in the central nervous system as well as psychiatric disorders. Interesting data is available which shows the effects of oxidative stress on psychological disorders. Major depressive disorder (MDD) is one of the consequences of an augmented lipid peroxidation [37-39].

Furthermore, oxidative stress can lead to attention deficit, autistic disorder, mental retardation, delirium, hyperactivity, dementia, schizophrenia, delusional disorders, disorders related to alcohol, nicotine dependence disorders, anxiety disorders, eating disorders and sleep disorders [40].

To explore the involvement of oxidative stress, approximately 190-193 disorders were selected. The selected mental disorders are recognized by The Diagnostic and Statistical Manual of Mental Disorders (DSM) and The International Statistical Classification of Diseases and Related Health Problems (ICD). DSM and ICD's list is approved by American Psychiatric Association (APA) and World Health Organization (WHO), respectively.

Different classical search terms like "oxidative stress affective disorders", "free radicals and neurodegenerative disorders", "oxidative stress and psychological disorders", "oxidative stress, free radicals and psychiatric disorders" and "association of oxidative stress" were used in conjunction with each of the DSM and ICD approved mental disorders. A broad spectrum of 83 degenerative syndromes and psychiatric disorders were identified. A table has been compiled which includes name of disorder, definition or characteristic of disorder (taken from online sources), specie (rats, mice and/or humans), and key biochemical parameter/s described or reported in detail in the given reference. For simplicity one reference per disorder has been added in the Table 1.

Precisely, Superoxide Dismutase (SOD), Catalase (CAT), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma Glutamyltransferase (Gamma-GT), Glutathione Peroxidase (GPX) Activities, Cholesterol, Triglyceride (TG), Uric Acid, Reactive Oxygen Species (ROS) Levels, Malondialdehyde (MDA), Oxidized Nucleic Acids, Tromboxane B2, Protein Carbonyls, Total Antioxidant Capacity (TAC), Paraoxonase (PON), Arylesterase (ARE) Antioxidant and 3-nitrotyrosine (3-NT), Selenium, Ascorbic/Dehydroascorbic Acid, Retinol, A-Tocopherol, Selenium-Dependent Glutathione Peroxidase, Reduced/Oxidized Glutathione, Glyoxalase 1 and Glutathione Reductase 1, Peroxidative Damage, High Levels of Proapoptotic Bax Expression, Low Levels Of Anti-apoptotic BCL-2 Expression, Cleavage of Death Substrate, Poly(ADP-ribose) Polymerase (PARP), Caspase-3, Stress Hormones, Cortisol, Dehydroepiandrosterone Sulphate (DHEAS), Thioredoxin (TRx), Creatine Phosphokinase (CPK), Leukocytosis, Ferroptosis, 8-hydroxy-2'-deoxyguanosine (8-OHdG), Succinate Dehydrogenase, Lactate Dehydrogenase, and NADPH Diaphorase, Mitochondrial Function and Redox State, 4-hydroxy-2-nonenal (4-HNE), Mitochondrial Membrane Potential, Mitochondrial Structure, 8-hydroxy-2'-deoxyguanosine (8-OHdG), Hexanoyl-lysine adduct (HEL), Acrolein-lysine adduct (ACR), F2-Isoprostanes,

Table 1. Association of oxidative stress with psychiatric disorders.

S#	Name of Disorder	Characteristic	Specie	Key Biochemical Parameter/s	Reference
1.	Aboulia	In neurology, refers to a lack of will or initiative and can be seen as a disorder of diminished motivation (DDM). Aboulia falls in the middle of the spectrum of diminished motivation, with apathy being less extreme and a kinetic mutism being more extreme than aboulia.	Review	Review	[41]
2.	Post Traumatic Stress Disorder	Posttraumatic stress disorder (PTSD) may develop after a person is exposed to one or more traumatic events, such as sexual assault, warfare, serious injury, or threats of imminent death. The diagnosis may be given when a group of symptoms, such as disturbing recurring flashbacks, avoidance or numbing of memories of the event, and hyperarousal, continue for more than a month after the occurrence of a traumatic event.	Human	Tromboxane B2, 8-OHdG and Protein Carbonyls, ROC Analysis	[42]
3.	Adjustment disorder	An adjustment disorder (AD) occurs when an individual is unable to adjust to or cope with a particular stressor, like a major life event. Since people with this disorder normally have symptoms that depressed people do, such as general loss of interest, feelings of hopelessness and crying, this disorder is sometimes known as situational depression.	Human	Protein Carbonyl , Nitrosylated Proteins	[43]
4.	Adolescent antisocial behavior	Anti-social behaviours are actions that harm or lack consideration for the well-being of others. Anti-social behaviour is labelled as such when it is deemed contrary to prevailing norms for social conduct.	Human	lead Levels, Lead Poisoning And Phosphorus Content	[44]
5.	Age-related cognitive decline	normal (non-pathological, normative, usual) cognitive ageing-is an important human experience which differs in extent between individuals.	Mice	SOD/CAT MIMICS, EUK-189 and EUK-207, Reactive Oxygen Species (ROS) Levels, Lipid Peroxidation And Oxidized Nucleic Acids	[45]
6.	Agoraphobia	Agoraphobia is an anxiety disorder characterized by anxiety in situations where the sufferer perceives certain environments as dangerous or uncomfortable, often due to the environment's vast openness or crowdedness. These situations include wide-open spaces, as well as uncontrollable social situations such as the possibility of being met in shopping malls, airports and on bridges.	Human	Total Antioxidant Capacity (TAC), Paraoxonase (PON), Arylesterase (ARE) Antioxidant And Malondialdehyde (MDA)	[46]
7.	Alcohol Abuse	is a psychiatric diagnosis describing the recurring use of alcohol despite its negative consequences. Alcohol abuse is sometimes referred to by the less specific term alcoholism.	Human	Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma Glutamyltransferase (Gamma-GT), and Levels of Cholesterol, Triglyceride (TG), and Uric Acid Serum Malondialdehyde (MDA) Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPX) Activities CAT	[47]

(Table 1) Contd....

S#	Name of Disorder	Characteristic	Specie	Key Biochemical Parameter/s	Reference
8.	Alcohol Withdrawal	is a set of symptoms that can occur when an individual reduces or stops alcoholic consumption after long periods of use. Prolonged and excessive use of alcohol leads to tolerance and physical dependence. The withdrawal syndrome is largely a hyper-excitability response of the central nervous system to lack of alcohol.	Human	MDA level SOD, CAT and GPX,	[48]
9.	Alzheimer's disease	accounts for 60% to 70% of cases of dementia. It is a chronic neurodegenerative disease that usually starts slowly and gets worse over time. The most common early symptom is difficulty in remembering recent events (short term memory loss). As the disease advances, symptoms can include: problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self care, and behavioural issues.	-	Review	[49]
10.	Amnesic disorder	The amnesic disorders are a group of disorders that involve loss of memories previously established, loss of the ability to create new memories, or loss of the ability to learn new information.	Human	HNE, a lipid peroxidation product, the levels of markers of protein oxidation, 3-nitrotyrosine (3-NT)	[50]
11.	Amphetamine dependence	Refers to a state of psychological dependence on a drug in the amphetamine class. In individuals with substance use disorder (problematic use or abuse with dependence), psychotherapy is currently the best treatment option as no pharmacological treatment has been approved	Rats	Superoxide Dismutase (SOD) and Catalase (CAT)	[51]
12.	Anorexia nervosa	Is an eating disorder characterized by immoderate food restriction, inappropriate eating habits or rituals, obsession with having a thin figure, and an irrational fear of weight gain. It is accompanied by a distorted body self-perception, and typically involves excessive weight loss.	Human	Selenium, Ascorbic/ Dehydroascorbic Acid, Retinol, A-Tocopherol, Selenium-Dependent Glutathione Peroxidase, Reduced/Oxidated Glutathione	[52]
13.	Anterograde amnesia	Is a loss of the ability to create new memories after the event that caused the amnesia, leading to a partial or complete inability to recall the recent past, while long-term memories from before the event remain intact.	Mice	Superoxide dismutase, Catalase And Glutathione Peroxidase, Malondialdehyde	[53]
14.	Antisocial personality disorder	Is characterized by a pervasive pattern of disregard for, or violation of, the rights of others. There may be an impoverished moral sense or conscience and a history of crime, legal problems, and impulsive and aggressive behavior.	Human	The Point Subtraction Aggression Paradigm	[54]
15.	Anxiety disorder	are a category of mental disorders characterized by feelings of anxiety and fear, where anxiety is a worry about future events and fear is a reaction to current events. These feelings may cause physical symptoms, such as a racing heart and shakiness.	Rats	Glyoxalase 1 and Glutathione Reductase 1	[55]
16.	Attention deficit disorder	is characterized primarily by inattentive concentration or a deficit of sustained attention, such as procrastination, hesitation, and forgetfulness; it differs in having fewer or no typical symptoms of hyperactivity or impulsiveness.	Human	Malondialdehyde (MDA), paraoxonase and arylesterase enzyme activities	[56]

(Table 1) Contd....

S#	Name of Disorder	Characteristic	Specie	Key Biochemical Parameter/s	Reference
17.	Attention deficit hyperactivity disorder	is a psychiatric disorder of the neurodevelopmental type in which there are significant problems of attention, hyperactivity, or acting impulsively that are not appropriate for a person's age.		Review	[57]
18.	Autism	is a neurodevelopmental disorder characterized by impaired social interaction, verbal and non-verbal communication, and restricted and repetitive behavior.	-	Review	[58]
19.	Asperger Syndrome	is an autism spectrum disorder (ASD) that is characterized by significant difficulties in social interaction and nonverbal communication, alongside restricted and repetitive patterns of behavior and interests. It differs from other autism spectrum disorders by its relative preservation of linguistic and cognitive development.	Human	Total Antioxidant Status (TAOS), non-enzymatic (glutathione And Homocysteine) and Enzymatic (Catalase, Superoxide Dismutase, And Glutathione Peroxidase) Antioxidants, And Lipid Peroxidation	[59]
20.	Barbiturate dependence	With regular use of barbiturates, barbiturate dependence develops. This in turn may lead to a need for increasing doses of the drug to get the original desired pharmacological or therapeutic effect. Barbiturate use can lead to both addiction and physical dependence, and as such they have a high potential for abuse.	Rats	Malondialdehyde and H ₂ O ₂ Generation and NADPH Oxidation	[60]
21.	Benzodiazepine dependence	is when one has developed one or more of either tolerance, withdrawal symptoms, drug seeking behaviors, such as continued use despite harmful effects, and maladaptive pattern of substance use, according to the DSM-IV. In the case of benzodiazepine dependence, the continued use seems to be associated with the avoidance of unpleasant withdrawal reaction rather than from the pleasurable effects of the drug.	Rats	Peroxidative Damage, High Levels Of Proapoptotic Bax Expression, And Low Levels Of Antiapoptotic BCL-2 Expression, Cleavage Of Death Substrate, Poly(ADP-ribose) Polymerase (PARP), and Activation Of A Key Effector Of Apoptosis, Caspase-3.	[61]
22.	Benzodiazepine withdrawal	is the cluster of <u>symptoms</u> that emerge when a person who has taken <u>benzodiazepines</u> , either as prescribed or abusively, and has developed a physical <u>dependence</u> undergoes dosage reduction or discontinuation. And is characterized by often severe sleep disturbance, irritability, increased tension and anxiety, panic attacks, hand tremor, sweating, difficulty with concentration, confusion and cognitive difficulty, memory problems, dry retching and nausea, weight loss, palpitations, headache, muscular pain and stiffness, a host of perceptual changes, hallucinations, seizures, psychosis, and suicide	Rats	TBARS SOD Glutathione Reductase (GR)	[62]
23.	Bereavement	is a multifaceted response to loss, particularly to the loss of someone or something that has died, to which a bond or affection was formed. Although conventionally focused on the emotional response to loss, it also has physical, cognitive, behavioral, social, spiritual, and philosophical dimensions.	Human	Stress Hormones, Cortisol And Dehydroepiandrosterone Sulphate (DHEAS).	[63]

(Table 1) Contd....

S#	Name of Disorder	Characteristic	Specie	Key Biochemical Parameter/s	Reference
24.	Bipolar disorder	is a mental disorder characterized by periods of elevated mood and periods of depression. The elevated mood is significant and is known as mania or hypomania depending on the severity or whether there is psychosis. During mania an individual feels or acts abnormally happy, energetic, or irritable. During periods of depression there may be crying, poor eye contact with others, and a negative outlook on life.	Human	Thioredoxin (TRX)	[64]
25.	Brief psychotic disorder	is a period of psychosis whose duration is generally shorter, non re-occurring, and not caused by another condition. The disorder is characterized by a sudden onset of psychotic symptoms, which may include delusions, hallucinations, disorganized speech or behavior, or catatonic behavior.	Human	Superoxide Dismutase, Glutathione Peroxidase, And Catalase	[65]
26.	Caffeine-induced sleep disorder	is a psychiatric disorder that results from overconsumption of the stimulant caffeine. "When caffeine is consumed immediately before bedtime or continuously throughout the day, sleep onset may be delayed, total sleep time reduced, normal stages of sleep altered, and the quality of sleep decreased.	Rats	Serum total protein and serum blood urea nitrogen levels, brain cholesterol and tryptophan levels.	[66]
27.	Cannabis dependence	is a condition characterized by the harmful consequences of repeated cannabis use, a pattern of compulsive cannabis use, and (sometimes) physiological dependence on cannabis This disorder is only diagnosed when cannabis use becomes persistent and causes significant academic, occupational or social impairment.	Human	ROS Generation	[67]
28.	Catatonic disorder	is a state of neurogenic motor immobility and behavioral abnormality manifested by stupor.	Human	<u>Creatine</u> Phosphokinase (CPK), Leukocytosis, And Ferropenia.	[68]
29.	Cocaine dependence	is a psychological desire to use cocaine regularly. Cocaine overdose may result in cardiovascular and brain damage such as constricting blood vessels in the brain, causing strokes and constricting arteries in the heart, causing heart attacks specifically in the central nervous system.	Rats	Reactive Oxygen Species Production, Superoxide Dismutase And Glutathione Peroxidase	[69]
30.	Cocaine intoxication	to the immediate effects of cocaine on the body. Although cocaine intoxication and cocaine dependence can be present in the same individual, they present with different sets of symptoms.	Rats	Superoxide Dismutase (SOD) Malondialdehyde (MDA) Levels	[70]
31.	Cognitive disorder	are a category of mental health disorders that primarily affect learning, memory, perception, and problem solving, and include amnesia, dementia, and delirium.	Human	Malonaldehyde (MDA), Glutathione Peroxidase (GPx), Glutathione Reductase (GR), and Glutathione S-Transferase (GST)	[71]
32.	Delirium tremens	also referred to as DTs, "the horrors", "the bottleache", "quart mania", "ork orks", "gallon distemper", "barrel fever", "the shakes", or "the fear") is an acute episode of delirium that is usually caused by withdrawal from alcohol, first described in 1813. Benzodiazepines are the treatment of choice for delirium tremens.	Human	8-hydroxy-2'-deoxyguanosine (8-OHdG),	[72]

(Table 1) Contd....

S#	Name of Disorder	Characteristic	Specie	Key Biochemical Parameter/s	Reference
33.	Depressive disorder	is a mental disorder characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities.	-	Review	[73]
34.	Desynchronosis	is a physiological condition which results from alterations to the body's circadian rhythms resulting from rapid long-distance transmeridian (east-west or west-east) travel on high-speed aircraft.	Rats	Succinate Dehydrogenase, Lactate Dehydrogenase, and NADPH Diaphorase	[74]
35.	Developmental coordination disorder	also known as developmental dyspraxia is a chronic neurological disorder beginning in childhood that can affect planning of movements and co-ordination as a result of brain messages not being accurately transmitted to the body. It may be diagnosed in the absence of other motor or sensory impairments like cerebral palsy, muscular dystrophy, multiple sclerosis or Parkinson's disease.	-	Review	[75]
36.	Down Syndrome	also known as trisomy 21, is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21. It is typically associated with physical growth delays, characteristic facial features, and mild to moderate intellectual disability.	Cell Models	Sod Gpx Thioredoxin 1 And Glutaredoxin 1	[76]
37.	Dysthymia	is a mood disorder consisting of the same cognitive and physical problems as in depression, with less severe but longer-lasting symptoms.	Rat	Lipid Oxidation Levels And Superoxide Dismutase And Catalase	[77]
38.	EDNOS	is an eating disorder that does not meet the criteria for anorexia nervosa or bulimia nervosa. Individuals with EDNOS usually fall into one of three groups: sub-threshold symptoms of anorexia nervosa or bulimia nervosa, mixed features of both disorders, or extremely atypical eating behaviors that are not characterized by either of the other established disorders	Human	Mitochondrial Function And Redox State	[78]
39.	Generalized anxiety disorder	is an anxiety disorder that is characterized by excessive, uncontrollable and often irrational worry, that is, apprehensive expectation about events or activities.	Human	Vitamins E (Alphatocopherol), C (Ascorbic Acid), and β -Carotene	[79]
40.	Hallucinogen-related disorder	are a chemically diverse group of drugs that cause changes in a person's thought processes, perceptions of the physical world, and sense of time passing.		Review	[80]
41.	Huntington's disease	is a neurodegenerative genetic disorder that affects muscle coordination and leads to mental decline and behavioral symptoms. Symptoms of the disease can vary between individuals and affected members of the same family, but usually progress predictably.	Mice	4-hydroxy-2-nonenal (4-HNE), mitochondrial membrane potential, mitochondrial structure, and synapse structure	[81]
42.	Hypomanic episode	is a mood state characterized by persistent disinhibition and pervasive elevated (euphoric) or irritable mood, as well as thoughts and behaviors that are consistent with such a mood state. It is most often associated with the bipolar spectrum.	Human	Oxidative Stress Index	[82]

(Table 1) Contd....

S#	Name of Disorder	Characteristic	Specie	Key Biochemical Parameter/s	Reference
43.	Hypochondriasis	refers to excessive preoccupancy or worry about having a serious illness. This debilitating condition is the result of an inaccurate perception of the condition of body or mind despite the absence of an actual medical condition.	Chromafin cells	Ascorbate	[83]
44.	Inhalant abuse	Inhalant abuse refers to the deliberate inhalation or sniffing of common products found in homes and communities with the purpose of "getting high.	-	Review	[84]
45.	Intellectual disability	also called intellectual development disorder (IDD) and formerly known as mental retardation (MR), is a neurodevelopmental disorder characterized by impaired intellectual and adaptive functioning which is defined by an IQ score below 70 as well as a delay in general daily living skills. Other common symptoms include speech delays and lack of social functioning. Down syndrome and Fragile X syndrome often overlap with ID.	Human	8-hydroxy-2'-deoxyguanosine (8-OHdG), hexanoyl-lysine adduct (HEL) and acrolein-lysine adduct (ACR)	[85]
46.	Intermittent explosive disorder	behavioral disorder characterized by explosive outbursts of anger, often to the point of rage, that are disproportionate to the situation at hand (i.e., impulsive screaming triggered by relatively inconsequential events). Impulsive aggression is unpremeditated, and is defined by a disproportionate reaction to any provocation, real or perceived. Some individuals have reported affective changes prior to an outburst (e.g., tension, mood changes, energy changes, etc.)	Rats	8-hydroxy-2'-deoxyguanosine and 8-isoprostane	[86]
47.	Insomnia	there is an inability to fall <u>asleep</u> or to stay asleep as long as desired	Human	Glutathione Peroxidase (GSH-Px), Superoxide Dismutase (SOD), and Myeloperoxidase (MPO) Activities and Levels of Reduced Glutathione (GSH) and Malondialdehyde (MDA)	[87]
48.	Major depressive disorder	A mental disorder characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities.	-	Review	[88]
49.	Male erectile disorder	Impotence is sexual dysfunction characterized by the inability to develop or maintain an erection of the penis during sexual activity	-	Review	[89]
50.	Manic episode	a distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood. This period of abnormal mood must last at least 1 week (or less if hospitalization is required).	Humans	Thiobarbituric Acid Reactive substances (TBARS), Superoxide Dismutase (SOD), Catalase (CAT), and Neuron-Specific Enolase (NSE)	[90]
51.	Mixed episode	When an individual experiences a discrete period during which characteristics of both major depressive and manic episodes are evident, it is classified as a mixed episode. The individual may be diagnosed with one of the bipolar disorders.	-	review	[91]
52.	Mood disorder	a disturbance in the person's <u>mood</u>		Review	[92]

(Table 1) Contd....

S#	Name of Disorder	Characteristic	Specie	Key Biochemical Parameter/s	Reference
53.	Neuroleptic-related disorder	a life-threatening neurological disorder most often caused by an adverse reaction to neuroleptic or antipsychotic drugs. NMS typically consists of muscle rigidity, fever, autonomic instability, and cognitive changes such as delirium, and is associated with elevated plasma creatine phosphokinase.		Review	[93]
54.	Nicotine withdrawal	the group of symptoms that occur upon the abrupt discontinuation or decrease in intake of nicotine. The effects of nicotine withdrawal can include anxiety, depression, feelings of restlessness or frustration, headaches, an increase in appetite and difficulty concentrating	Rats	Dopamine, Norepinephrine and Serotonin	[94]
55.	Obsessive-compulsive disorder (OCD)	Common psychiatric disorder marked by obsessions and/or compulsions that are egodystonic and cause significant distress to the patients and their families	Human	Serum Thiobarbituric Acid Reacting Substances As Well As A Lower Plasma Ascorbates	[95]
56.	Opioid dependence	Opioid dependence is a medical diagnosis characterized by an individual's inability to stop using opiates (morphine, heroin, codeine, oxycodone, hydrocodone, etc.) even when objectively it is in his or her best interest to do so, and is a major component of opioid addiction.	-	Review	[96]
57.	Opioid-related disorder	Characterized by the harmful consequences of repeated opioid use, a pattern of compulsive opioid use, and (sometimes) physiological dependence on opioid (i.e., tolerance and/or symptoms of withdrawal). This disorder is only diagnosed when opioid use becomes persistent and causes significant academic, occupational or social impairment.	-	Review	[97]
58.	Pain disorder	Chronic pain experienced by a patient in one or more areas, and is thought to be caused by psychological stress. The pain is often so severe that it disables the patient from proper functioning. Duration may be as short as a few days or as long as many years.	Human	Malondialdehyde and F2-Isoprostanes 8-hydroxy-2-deoxyguanosine	[98]
59.	Panic disorder	an anxiety disorder with a chronic course characterized by recurrent, unexpected panic attacks and a series of long-term signs and behaviors between the attacks	Human	Glutathione Peroxidase (GSH-Px), Superoxide Dismutase (SOD) And Catalase (CAT) And Malondialdehyde (MDA)	[99]
60.	Parkinson's Disease	Associated with a selective loss of the neurons in the midbrain area called the substantia nigra pars compacta. These neurons contain the neurotransmitter dopamine (DA), and their projecting nerve fibers reside in the striatum	-	Review	[100]
61.	Phobic disorder	Collectively, phobic disorders (including social anxiety disorder [social phobia], specific phobia, and agoraphobia) are the most common forms of psychiatric illness, surpassing the rates of mood disorders and substance abuse. Severity can range from mild and unobtrusive to severe and can result in incapacity to work, travel, or interact with others.	Human	Fluorescent Oxidation Products (FLOPs).	[101]

(Table 1) Contd....

S#	Name of Disorder	Characteristic	Specie	Key Biochemical Parameter/s	Reference
62.	Posttraumatic stress disorder (PTSD)	an anxiety disorder that can develop in response to real or perceived life-threatening situations.	Rats	Eactive Oxygen Species And Inflammatory Cytokines	[102]
63.	Primary insomnia	Primary insomnia, simply called insomnia, is a common sleep disorder that affects most adults at some point in their lives. People with insomnia typically have trouble falling or staying asleep. In some cases, insomniacs fall asleep quickly, but wake up several times throughout the night.	Humans	Glutathione Peroxidase (GSH-Px), Superoxide Dismutase (SOD), and Myeloperoxidase (MPO) Activities and Levels of Reduced Glutathione (GSH) and Malondialdehyde (MDA)	[103]
64.	Psychological factor affecting medical condition	This term is classified under "other conditions" and is used when specific psychological factors are judged to interfere with treatment, affect the course, add to the associated risk, or exacerbate symptoms of a general medical condition. These can include any of the mental disorders as well as symptoms and personality traits.	-	Review	[104]
65.	Psychotic disorder	Psychotic disorders are severe mental disorders that cause abnormal thinking and perceptions. People with psychoses lose touch with reality. Two of the main symptoms are delusions and hallucinations. Delusions are false beliefs, such as thinking that someone is plotting against you or that the TV is sending you secret messages. Hallucinations are false perceptions, such as hearing, seeing, or feeling something that is not there.	Humans	Metabolomic Profiling	[105]
66.	Recurrent brief depression	Characterized by frequently occurring brief depressive episodes, lasting less than two weeks, is now recognised as a common and disabling illness with a chronic relapsing course and a significant suicide risk.	Humans	Superoxide Dismutase (SOD)	[106]
67.	Stress	Stress is a normal physical response to events that make you feel threatened or upset your balance in some way. When you sense danger—whether it's real or imagined—the body's defenses kick into high gear in a rapid, automatic process known as the "fight-or-flight-or-freeze" reaction, or the <i>stress response</i> .	-	Review	[107]
68.	Schizoaffective disorder	a mental disorder characterized by abnormal thought processes and deregulated emotions. The diagnosis is made when the patient has features of both schizophrenia and a mood disorder—either bipolar disorder or depression—but does not strictly meet diagnostic criteria for either alone. The bipolar type is distinguished by symptoms of mania, hypomania, or mixed episode; the depressive type by symptoms of depression only. Common symptoms of the disorder include hallucinations, paranoid delusions, and disorganized speech and thinking.	Humans	Total Oxidant Status (TOS) and Total Antioxidant Status (TAS)	[108]
69.	Schizophrenia	devastating mental disorder, expressed in the form of abnormal mental functions and disturbed behavior.	-	Review	[109]
70.	Severe mental retardation	is a neurodevelopmental disorder characterized by impaired intellectual and adaptive functioning which is defined by an IQ score below 70 as well as a delay in general daily living skills. Other common symptoms include speech delays and lack of social functioning.	Rats	Lipid Peroxidation, Sulfhydryl Oxidation	[110]

(Table 1) Contd....

S#	Name of Disorder	Characteristic	Specie	Key Biochemical Parameter/s	Reference
71.	Sleep disorder	a medical disorder of the sleep patterns of a person or animal. Disruptions in sleep can be caused by a variety of issues, from teeth grinding (bruxism) to night terrors. When a person suffers from difficulty falling asleep and/or staying asleep with no obvious cause, it is referred to as insomnia.	-	Review	[111]
72.	Sleep paralysis	phenomenon in which a person, either falling asleep or awakening, temporarily experiences an inability to move, speak or react. It is a transitional state between wakefulness and sleep characterized by complete muscle atonia (muscle weakness). Sleep paralysis has been linked to disorders such as narcolepsy, migraines, anxiety disorders, and obstructive sleep apnea; however, it can also occur in isolation.	Rats	Glyoxalase (GLO)-1 and Glutathione reductase (GSR)-1	[112]
73.	Social anxiety disorder	most common anxiety disorder. It is one of the most common psychiatric disorders, with 12% of American adults having experienced it in their lifetime. It is characterized by intense fear in one or more social situations, causing considerable distress and impaired ability to function in at least some parts of daily life.	Rats	Oxidative Stress Measurement, Inflammatory Markers (Interleukin (IL)-6), Glyoxalase (GLO)-1, Glutathione Reductase (GSR)-1	[113]
74.	Social phobia	Social phobia (also called social anxiety) is a type of anxiety problem. Extreme feelings of shyness and self-consciousness build into a powerful fear. As a result, a person feels uncomfortable participating in everyday social situations.	Humans	Malondialdehyde (MDA), Superoxide Dismutase (SOD), Glutathione Peroxidase (GSH-Px), Catalase (CAT)	[55]
75.	Somatization disorder	Somatization disorder is a long-term (chronic) condition in which a person has physical symptoms that involve more than one part of the body, but no physical cause can be found. The pain and other symptoms people with this disorder feel are real, and are not created or faked on purpose (malingering).	-	Review	[114]
76.	Specific phobia	A specific phobia is any kind of anxiety disorder that amounts to an unreasonable or irrational fear related to exposure to specific objects or situations. As a result, the affected person tends to actively avoid direct contact with the objects or situations and, in severe cases, any mention or depiction of them. The fear can, in fact, be disabling to their daily lives.	Mice	Glyoxalase 1 And Glutathione Reductase 1, Genetic Manipulation Using Lentivirus-Mediated Gene Transfer	[115]
77.	Stereotypic movement disorder	motor disorder with onset in childhood involving repetitive, nonfunctional motor behavior (e.g., hand waving or head banging), that markedly interferes with normal activities or results in bodily injury.	?	Inflammation And Immunity, Immunotherapy	[116]
78.	Stuttering	is a speech disorder in which the flow of speech is disrupted by involuntary repetitions and prolongations of sounds, syllables, words or phrases as well as involuntary silent pauses or blocks in which the person who stutters is unable to produce sounds.		Review	[117]

(Table 1) Contd....

S#	Name of Disorder	Characteristic	Specie	Key Biochemical Parameter/s	Reference
79.	Tardive dyskinesia	is a difficult-to-treat and often incurable form of dyskinesia, a disorder resulting in involuntary, repetitive body movements. In this form of dyskinesia, the involuntary movements are tardive, meaning they have a slow or belated onset. This neurological disorder most frequently occurs as the result of long-term or high-dose use of antipsychotic drugs, or in children and infants as a side effect from usage of drugs for gastrointestinal disorders.	Human	Superoxide Dismutase, Lipid Hydroperoxide, Protein Carbonyl Groups	[118]
80.	Transient global amnesia	neurological disorder whose key defining characteristic is a temporary but almost total disruption of short-term memory with a range of problems accessing older memories. A person in a state of TGA exhibits no other signs of impaired cognitive functioning but recalls only the last few moments of consciousness, as well as deeply encoded facts of the individual's past, such as their own name.	Rats	Malondialdehyde (MDA), 8-Iso-Prostaglandin F2alpha, Catalase And Superoxide Dismutase	[119]
81.	Tourette syndrome	an inherited neuropsychiatric disorder with onset in childhood, characterized by multiple physical (motor) tics and at least one vocal (phonic) tic. These tics characteristically wax and wane, can be suppressed temporarily, and are preceded by a premonitory urge. Tourette's is defined as part of a spectrum of tic disorders, which includes provisional, transient and persistent (chronic) tics.	Human	Anterior Cingulate Cortex (ACC), Striatum, Striatal Glutathione (GSH)	[120]
82.	Trichotillomania	An impulse disorder characterized by the compulsive urge to pull out one's hair, leading to noticeable hair loss and balding, distress, and social or functional impairment.	Mice	N-Acetylcysteine (NAC), Oxidative Stress Levels	[121]
83.	White coat hypertension	Phenomenon in which patients exhibit elevated blood pressure in a clinical setting but not in other settings. It is believed that this is due to the anxiety some people experience during a clinic visit.	Human	Serum PON1 Activity, oxLDL and Malondialdehyde (MDA)	[12114]

8-hydroxy-2-deoxyguanosine, Fluorescent Oxidation Products (FLOPs). Genetic Manipulation Using Lentivirus-Mediated Gene Transfer and *N*-Acetylcysteine (NAC) are some of the key enzymatic, non-enzymatic and genetic experimental features employed to associate oxidative stress with psychological disorders.

CONCLUSION

Andersen in 2004 [122] covered and provided detail information, whether oxidative stress is cause or consequence of neurodegenerative process. The question is still debatable. However, the literature indicates and precisely we provided a detail table and information with concrete references that oxidative stress is or can be associated with different psychological disorders. In the same vein the antioxidant therapy can not be excluded to atleast or partially overhaul the psychological stress or disorders. Dietary antioxidants, vitamin C, rutin, caffeic acid, rosmarinic acid [123], polyphenols, flavonoids [124], specific foods [125] and diets rich in sucrose and honey [126] have shown to possess not only antioxidant potential but also contributed significantly toward psychological stress or disorders. Interestingly, classical antidepressants like citalopram, have shown antioxidant activity in patients with social phobia [123]. Similarly, data on synthetic antioxidants and or-

ganoselenium compounds as potential candidate drugs against psychological disorder have been reported in the literature [127-132]. The combinational use of antioxidants and anxiolytics or antidepressant may be interesting and promising, but more intensive research like proteomics, genomics, transcriptomics, pharmacological and toxicological insights are needed for proposed therapeutic applications.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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