DECLARATION

I hereby declare that this submission is my own work towards the MSc. and that, to the best of my knowledge, it contains no material previously published by another person, nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

Edward Essuman Eyipe ……. …….
PG4934910

Dr. W.K.B.A OWIREDU ……. …….
(Supervisor)

Dr. Yaw Osei ……. …….
(Co-Supervisor)

Dr. R.A Ngala ……. …….
(Head of Department)

ABSTRACT

The pathogenesis of a number of diseases like Psychiatric disorders, cardiovascular diseases, diabetes and cancer has been associated with changes in the balance of certain trace elements. Many disorders of the body are related to the altered serum mineral and trace element levels. It is indicative that there is an association between increased oxidative stress and the majority of psychiatric disorders which correlate with the integration of fatty acids and antioxidants, whether from a dietary-habit point of view or from a therapeutic point of view. The question therefore arises whether treatment of psychiatric patients will lead to trace elements dysmetabolism and subsequently oxidative stress. The aim of this study was to estimate trace element (Cu, Zn, Se, Mn, Fe, As, Li, and Cd) levels, oxidative stress and risk factors associated with Psychiatric disorders. In all, one hundred hundred (100) subject were included in the study; fourty (40) treatment naïve, fourty (40) patients receiving medication and twenty (20) control group. The subjects were recruited from the Psychiatric Unit of the Komfo Anokye teaching hospital. Among the three studied population, there was a significant difference in their systolic blood pressure (p=0.0135). Treatment Naïve patients significantly weighed lesser (57.38±1.65) than patients on treatment (69.69±1.76) and the control group (65.80±2.25) (p<0.0001). The mean body mass index of treatment Naïve patient (22.99±0.71) was lower compare to the patient s on treatment (26.56±0.69) and control (23.00±1.08) (p=0.0016). The mean concentrations of copper levels among treatment naïve patient (0.39±0.03) were significantly lower than patients on treatment (0.44±0.03) and the control (0.56±0.05) with a p value of 0.003. Copper levels correlated negatively to a small size effect with zinc levels in treatment naïve patients.The mean concentrations of vitamin E in treatment naïve patient (7.67±0.31) were significantly lower than that of the patient receiving treatment (9.98±0.26) and the control group (11.98±0.28) (p< 0.0001). Malondialdehyde levels were also significantly higher in treatment naïve patient (0.77±0.02) than the patient on treatment (0.69±0.02) and the control (0.66±0.02) (p<0.0001). Selenium levels of treatment naïve patients did not show any correlations with the trace elements, except for zinc in large size effect and iron medium size effect but in patient receiving medication, selenium levels correlated positively with vitamin C in a medium size effect. It is clear from this study that during the progression of psychiatric disorders, there is a concomitant induction of cellular oxidative stress characterized by; an increase in Malodialdehyde (MDA), a product from lipid peroxidation and reduced scavenging activities of vitamin C and E. It is further recommended that studies are done to establish the relationship between Selenium Copper, Zinc and Cadmium among psychiatric patients.

ACKNOWLEDGEMENT

My greatest gratitude goes to the almighty God for seeing me through the programme.

I wish to express my profound gratitude to my supervisor Dr. W.K.B.A. Owiredu of the Department of Molecular Medicine, KNUST, for the supervision and above all the inspiration that made this project a reality.

I am indepted to Dr Yaw Osei of the Psychiatric Unit of the Komfo Anokye Teaching Hospital and who welcomed me to his department and co-supervised me to the best of his ability.

My sincere gratitude also goes to Dr Chris Obirikorang, Senior JOY, and indeed all my lecturers at the Department of Molecular Medicine, KNUST for the useful suggestions, not forgetting Mr. Prosper of Molecular Medicine Lab and Unkle Nash of Atomic Energy chemistry Department.

I am also grateful to, Derick Afful, Afrifa IV and Jubilant Abledu for their technical support.

Finally, my heartfelt gratitude goes to Mr J E Essuman, Rhoda E Essuman and Jennifer Samanhyia; my family and all the wonderful friends who were not mentioned for want of space.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ADHD	-	Attention Deficit Hyperactivity Disorder
ALS	-	Amyotrophic lateral Sclerosis
ANOVA	-	Analysis of Variance
APA	-	American Psychiatric Association
CPNS	-	Community Psychiatry Nurses School
CVD	-	Cardiovascular Disease
D2	-	Dopamine Receptor
DNA	-	Deoxyribonucliec Acid
DSM	-	Diagnostic and Statistical Manual of Mental Disorders
FGAs	-	First Generation Antipsychotics
GRd	-	Gluthathione reductase
GSH-PX	-	Gluthathione Peroxidase
HIV	-	Humman Immunodeficiency Virus
H_2O_2	-	Hydrogen Peroxide
HPLC	-	High-Performance Liquid Chromatography
ICD	-	International Classification of Disease
IDF	-	International Diabetes Federation
LPO	-	Lipid Peroxidation

MARATA	-	Multi-Acting Receptor-Targeted Antipsychotics
MDA	-	Malondialdehyde
NADPH	-	Nicotinamide Adenine Dinucleotide Phosphate
NICE	-	National Institute for Health and Clinical Excellence
NMDA	-	N-Methyl-D-Aspartate Receptor
OCD	-	Obsessive Compulsive Disorder
PTFE	-	Polytetraflouroethylene
PUFAs	-	Polyunsaturated Fatty Acids
ROS	-	Reactive Oxygen Species
RNS	-	Reactive Nitrogen Species
SGAs	-	Second Generation Antipsychotics
SOD	-	Superoxide Dismutase
TBA	-	Thiobarbituric Acid
TCA	-	Thiochloroacetic Acid
US	-	United State
UK	-	United Kingdom
WHO	-	World Health Organization
QRN	-	Qualified Registered Mental Nursing

Chapter 1

INTRODUCTION

1.1 BACKGROUND

Minerals and trace elements are necessary for both physiological and biochemical functions. Many disorders of the body are related to the altered serum mineral and trace element levels. Trace elements are usually defined as minerals that are required in amounts between 1 and 100 mg/day by adults or make up less than 0.01% of total body weight. Deficiency of essential trace elements or minerals and excess of potentially harmful trace elements or minerals are both known to have adverse effects in the general population (Asare *et al*, 2010).

It is indicative that there is an association between increased oxidative stress and the majority of psychiatric disorders which correlate with the integration of fatty acids and antioxidants, whether from a dietary-habit point of view or from a therapeutic point of view (Tsaluchidu *et al*, 2008).

The long hydrocarbon chain of polyunsaturated fatty acids in membrane phospholipids has kinks at the site of *cis* double bonds which, as a result of the stearic effects created, provides remarkable reactivity to the molecule. Owing to the fluidity of the lipid component, the biomolecules demonstrate a notable degree of mobility, thereby helping to explain their functional properties.

Neuronal membrane phospholipids are particularly susceptible to peroxidation mediated by oxyradicals, that is, by reactive oxygen species (ROS). These constitute a highly reactive species, owing to the presence of unpaired outer shell electrons, and are generated both through aerobic metabolic physiological processes and through pathological processes which may be ischaemic, inflammatory, or caused by emotional or psychological stress or environmental pollution, smoking or poor dietary habits.

Trace elements are incorporated into enzymes and complex carbohydrates. Copper is a cofactor for numerous enzymes and plays an important role in development

(Desai and Kaler., 2008). Zinc is important for the functioning of more than 300 enzymes from all six enzyme classes and some of them are involved with DNA and RNA synthesis (Vallee *et al*., 1991; Tudor *et al*., 2005; Vallee and Falchuk, 1993). Furthermore, zinc plays a vital role in the immune system and is essential for the optimal function of a variety of physiological and biochemical processes (Tudor *et al*., 2005). The pathogenesis of a number of diseases like Psychiatric disorders, cardiovascular diseases, diabetes and cancer has been associated with changes in the balance of certain trace elements. Trace elements are essential for numerous metabolic and physiological processes in the body (Merz, 1981). Therefore, imbalances in the optimum levels of trace elements may affect biological processes and have been associated with many diseases including heart autoimmune, cancer, renal failure and neurological disorders (Shokrzadeh *et al*., 2009). Most of these diseases have been associated with changes in the balance of trace elements like manganese (Mn), copper (Cu), zinc (Zn), calcium (Ca), iron (Fe) et cetra. Mn, Zn, Fe and Cu accomplish decisive functions in maintaining human health and play an important role in the synthesis and structural stabilization of both proteins and nucleic acids (Fraga 2005). The question therefore arises whether treatment of psychiatric patients will lead to trace elements dysmetabolism and subsequently oxidative stress.

1.2 HYPOTHESIS

There is no association between Psychiatric disorders, oxidative stress and trace element dysmetabolism

1.3 AIM OF STUDY

This study aims to assess the effect of trace elements dysmetabolism and oxidative stress in psychiatric patients.

1.4 SPECIFIC OBJECTIVES

- To determine serum trace element dysmetabolism including Copper, Zinc, Selenium, Arsenic, Cadmium, Manganese Lithium and iron in Psychiatric Patients.
- To determine levels of oxidative stress among Psychiatric Patients
- To determine whether substance abuse is a risk factor to Psychiatric Induced Oxidative stress.

1.5 JUSTIFICATION OF STUDY

In general, oxidative stress is the overpowering of anti-oxidant defense system by oxidative system caused by overproduction of ROS. At present, many lines of evidence from animal and human studies suggest that mitochondrial dysfunction is the main source of ROS that have a central role in pathogenesis of neurodegenerative diseases (Hadjigeorg., 2008). Psychiatric disorders are on the increase in Ghana (Turkson, 1998) due to the abuse of psychoactive substances such as cannabis heroin etc. Owiredu *et al* (2009) in a study to determine the impact of blood glucose and cholesterol levels on the manifestation of psychiatric disorders found the prevalence of diabetes to be associated with antipsychotic agents. Many research works done have linked oxidative stress with Psychiatric disorders such as schizophrenia in which there is an increase in levels of ethane which is a direct maker of n-3 lipid peroxidation (Puri *et al*., 2008). Increased oxidative stress, associated with increased lipid peroxidation (LPO), reinforces the possibility that dietary supplementation with the essential trace elements may be helpful in the therapy of psychiatric disorders such as schizophrenia, depression, Huntington's disease and attention- deficit hyperactivity disorder.

Chapter 2

LITERATURE REVIEW

2.1 DEFINITION OF PSYCHIATRIC DISORDER

A mental disorder or mental illness is a psychological or behavioral pattern associated with distress or disability that occurs in an individual and is not a part of normal development or culture (Owiredu *et al.,* 2012). Pednault (2009) also defined psychiatric disorder as any pattern of psychological or behavioral symptoms that causes an individual significant distress, impairs their ability to function in life, and/or significantly increases their risk of death, pain, disability, or loss of freedom.

Mental disorders are conceptualized as disorders of brain circuits probably caused by developmental processes shaped by a complex interplay of genetics and experience. The genetics of mental illness may therefore really be the genetics of brain development, with different outcomes possible, depending on biological and environmental context (Insel and Wang, 2010). The recognition and understanding of mental health conditions has changed over time and across cultures and there are still variations in the definition, assessment and classification of mental disorders, although standard guidelines criteria are widely accepted.

2.2 CLASSIFICATION OF PSYCHIATRIC DISORDERS

The definition and classification of Psychiatric disorders is a key issue for mental health and for users and providers of mental health services. There are currently two widely established systems that classify mental disorders- ICD-10 Chapter V: Mental and behavioural disorders, part of the International Classification of Diseases produced by the World Health Organization (WHO), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) produced by the American Psychiatric Association (APA). These manuals list categories of disorder and provide standardized criteria for diagnosis

(Voices.yahoo.com/psychological-disorders). They have converged their codes in recent revisions so that the manuals are often broadly comparable, although significant differences remain. Other classification schemes may be used in non-western cultures (e.g. the Chinese Classification of Mental Disorders), and other manuals may be used by those of alternative theoretical persuasions, e.g. the Psychodynamic Diagnostic Manual.

The following is a brief classification of psychiatric disorders as explained in detailed by Owiredu et al (2012).

- **Anxiety disorder**, different forms of abnormal and pathological fear and anxiety
- **Conversion disorder**, neurological symptoms such as numbness, blindness, paralysis, or fits, where no neurological explanation is possible
- **Mental disorder**, a psychological or behavioral pattern associated with distress or disability that occurs in an individual and is not a part of normal development or culture
- **Obsessive-compulsive personality disorder**, obsession with perfection, rules, and organization
- **Personality disorder**, an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the culture of the individual who exhibits it. There are many different categories of mental disorder, and many different facets of human behavior and personality that can become disordered (Gazzinga et al., 2006).

2.2.1 Anxiety or fear

This interferes with normal functioning and may be classified as an anxiety disorder (Akiskal *et al*., 2006). Commonly recognized categories include specific phobias, generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, obsessive-compulsive disorder and post-traumatic stress disorder. Other affective (emotion/mood) processes can also become disordered. Mood disorder involving unusually intense and sustained sadness,

melancholia, or despair is known as major depression (also known as unipolar or clinical depression). Milder but still prolonged depression can be diagnosed as dysthymia. Bipolar disorder (also known as manic depression) involves abnormally "high" or pressured mood states, known as mania or hypomania, alternating with normal or depressed mood. The extent to which unipolar and bipolar mood phenomena represent distinct categories of disorder, or mix and merge along a dimension or spectrum of mood, is subject to some scientific debate (Morey *et al*., 2007).

2.2.2 *Patterns of belief, language use and perception of reality*

Patterns of belief, language use and perception of reality can become disordered (e.g., delusions, thought disorder, hallucinations). Psychotic disorders in this domain include schizophrenia, and delusional disorder. Schizoaffective disorder is a category used for individuals showing aspects of both schizophrenia and affective disorders. Schizotypy is a category used for individuals showing some of the characteristics associated with schizophrenia but without meeting cutoff criteria (Alonso *et al*., 2004).

2.2.3 *Personality*

The fundamental characteristics of a person that influence thoughts and behaviors across situations and time—may be considered disordered if judged to be abnormally rigid and maladaptive. Although treated separately by some, the commonly used categorical schemes include them as mental disorders, albeit on a separate "axis II" in the case of the DSM. A number of different personality disorders are listed, including those sometimes classed as "eccentric", such as paranoid, schizoid and schizotypal personality disorders; types that have been described as "dramatic" or "emotional", such as antisocial, borderline, histrionic or narcissistic personality disorders; and those sometimes classed as fear-related, such as anxious-avoidant, dependent,

or obsessive-compulsive personality disorders. The personality disorders in general are defined as emerging in childhood, or at least by adolescence or early adulthood. The ICD also has a category for enduring personality change after a catastrophic experience or psychiatric illness. If an inability to sufficiently adjust to life circumstances begins within three months of a particular event or situation, and ends within six months after the stressor stops or is eliminated, it may instead be classed as an adjustment disorder. There is an emerging consensus that so-called "personality disorders", like personality traits in general, actually incorporate a mixture of acute dysfunctional behaviors that may resolve in short periods, and maladaptive temperamental traits that are more enduring (Gamma *et al.*, 2007). Furthermore, there are also non-categorical schemes that rate all individuals via a profile of different dimensions of personality without a symptom-based cutoff from normal personality variation, for example through schemes based on dimensional models (Mental Health., 2009).

2.2.4 Eating And Sleeping disorders

This involves disproportionate concern in matters of food and weight (Clark 2007). Categories of disorder in this area include anorexia nervosa, bulimia nervosa, exercise bulimia orbinge eating disorder. Sleep disorders such as insomnia involve disruption to normal sleep patterns, or a feeling of tiredness despite sleep appearing normal.

2.2.5 Sexual and impulse control Disorders

Sexual and gender identity disorders may be diagnosed, including dyspareunia, gender identity disorder and ego-dystonic homosexuality. Various kinds of paraphilia are considered mental disorders (sexual arousal to objects, situations, or individuals that are considered abnormal or harmful to the person or others).

People who are abnormally unable to resist certain urges or impulses that could be harmful to themselves or others, are classed as having an impulse control disorder, including various kinds of tic disorders such as Tourette's syndrome, and disorders such as kleptomania (stealing) or pyromania (fire-setting). Various behavioral addictions, such as gamblingaddiction, may be classed as a disorder (Akiskal *et al*., 2006).

2.2.6 Obsessive-compulsive and substance use disorder

Obsessive-compulsive disorder can sometimes involve an inability to resist certain acts but is classed separately as being primarily an anxiety disorder.

The use of drugs (legal or illegal, including alcohol), when it persists despite significant problems related to its use, may be defined as a mental disorder. The DSM incorporates such conditions under the umbrella category of substance use disorders, which includes substance dependence and substance abuse. The DSM does not currently use the common term drug addiction, and the ICD simply refers to "harmful use". Disordered substance use may be due to a pattern of compulsive and repetitive use of the drug that results in tolerance to its effects and withdrawal symptoms when use is reduced or stopped.

2.2.7 Memory and cognitive disorders

People who suffer severe disturbances of their self-identity, memory and general awareness of themselves and their surroundings may be classed as having a dissociative identity disorder, such as depersonalization disorder or Dissociative Identity Disorder itself (which has also been called multiple personality disorder, or "split personality"). Other memory or cognitive disorders include amnesia or various kinds of old age dementia **(**The United States Department of Health and Human Services**)**.

A range of developmental disorders that initially occur in childhood may be diagnosed, for example autism spectrum disorders, oppositional defiant

disorder and conduct disorder, and attention deficit hyperactivity disorder (ADHD), which may continue into adulthood (Akiskal *et al*., 2006).

2.2.8 Conduct and somatoform disorders

Conduct disorder, if continuing into adulthood, may be diagnosed as antisocial personality disorder (dissocial personality disorder in the ICD). Popularist labels such as psychopath (or sociopath) do not appear in the DSM or ICD but are linked by some to these diagnoses.

Somatoform disorders may be diagnosed when there are problems that appear to originate in the body that are thought to be manifestations of a mental disorder. This includes somatization disorder and conversion disorder. There are also disorders of how a person perceives their body, such as body dysmorphic disorder. Neurasthenia is an old diagnosis involving somatic complaints as well as fatigue and low spirits/depression, which is officially recognized by the ICD-10 but no longer by the DSM-IV (Gamma et al., 2007).

2.2.9 Factitious and other disorders

This include disorders such as *Munchausen syndrome*, are diagnosed where symptoms are thought to be experienced (deliberately produced) and/or reported (feigned) for personal gain.

There are attempts to introduce a category of relational disorder, where the diagnosis is of a relationship rather than on any one individual in that relationship. The relationship may be between children and their parents, between couples, or others. There already exists, under the category of psychosis, a diagnosis of shared psychotic disorder where two or more individuals share a particular delusion because of their close relationship with each other.

There are a number of uncommon psychiatric syndromes, which are often named after the person who first described them, such as Capgras syndrome, De Clerambault syndrome, Othello syndrome, Ganser

syndrome, Cotard delusion, and Ekbom syndrome, and additional disorders such as the Couvade syndrome and Geschwind syndrome (Trimble., 2001).

Various new types of mental disorder diagnosis are occasionally proposed. Among those controversially considered by the official committees of the diagnostic manuals include self-defeating personality disorder, sadistic personality disorder, passive-aggressive personality disorder and premenstrual dysphoric disorder.

Two recent unique unofficial proposals are solastalgia by Glenn Albrecht and hubris syndrome by David Owen. The application of the concept of mental illness to the phenomena described by these authors has in turn been critiqued by Mac Suibhne (2009).

2.3 PSYCHIATRIC DISORDERS GLOBALLY

Globally more than one in three people in most countries report sufficient criteria for at least one at some point in their life since psychiatric disorders are common. (WHO International Consortium in Psychiatric Epidemiology., 2000). In the United States 46% qualified for a mental illness at some point (Kessler. 2005). A survey by the World Mental Health Survey Initiative (2010) indicates that anxiety disorders are the most common in all but one country, followed by mood disorders in all but two countries, while substance disorders and impulse-control disorders were consistently less prevalent.

A review of anxiety disorder surveys in different countries found average lifetime prevalence estimates of 16.6%, with women having higher rates on average. (Somers et al 2006)

A review of mood disorder surveys in different countries found lifetime rates of 6.7% for major depressive disorder (higher in some studies, and in women) and 0.8% for Bipolar I disorder (Waraich., 2004)

In the United States the frequency of disorder is: anxiety disorder (28.8%), mood disorder (20.8%), impulse-control disorder (24.8%) or substance use disorder (14.6%) (Kessler., 2005).

A 2004 cross-Europe study found that approximately one in four people reported meeting criteria at some point in their life for at least one of the DSM-IV disorders assessed, which included mood disorders (13.9%), anxiety disorders (13.6%) or alcohol disorder (5.2%). Approximately one in ten met criteria within a 12-month period. Women and younger people of either gender showed more cases of disorder (US National Institute of Mental Health., 2006). A 2005 review of surveys in 16 European countries found that 27% of adult Europeans were affected by at least one mental disorder in a 12 month period (Alonso *et al*., 2004).

An international review of studies on the prevalence of schizophrenia found an average (median) figure of 0.4% for lifetime prevalence; it was consistently lower in poorer countries (Wittchen *et al*., 2005).

Studies of the prevalence of personality disorders (PDs) have been fewer and smaller-scale, but one broad Norwegian survey found a five-year prevalence of almost 1 in 7 (13.4%). Rates for specific disorders ranged from 0.8% to 2.8%, differing across countries, and by gender, educational level and other factors (Saha *et al*., 2005). A US survey that incidentally screened for personality disorder found a rate of 14.79% (Torgersen *et al*., 2001).

Approximately 7% of preschool pediatric sample were given a psychiatric diagnosis in one clinical study, and approximately 10% of 1- and 2-year-olds receiving developmental screening have been assessed as having significant emotional/behavioral problems based on parent and pediatrician reports (Grant *et al*., 2004)

While rates of psychological disorders are often the same for men and women, women tend to have a higher rate of depression. Each year 73 million women are

afflicted with major depression, and suicide is ranked 7th as the cause of death for women between the ages of 20-59. Depressive disorders account for close to 41.9% of the disability from neuropsychiatric disorders among women compared to 29.3% among men (Carter *et al*., 2004).

2.4 BRIEF HISTORY OF MENTAL HEALTH IN GHANA

Legal backing to mental health activities started with the enactment of the Lunatic Asylum Ordinance in 1888 signed by the then Governor of the Gold Coast, Sir Griffith Edwards. Before this period, the mentally ill were found roaming in towns, villages, bushes and some locked up either in their homes or restrained by native doctors. With the enactment of the ordinance, those who were found to be mentally ill were labelled "insane", arrested and put in a special prison in the capital Accra (owiredu *et al*., 2012). By the beginning of the 20th Century, this prison had become full and therefore a facility named "The Lunatic Asylum, presently known as the Accra Psychiatric hospital was built in 1906. Owiredu et al (2012) continue to report that the first psychiatrist south of the Sahara Dr. E.F.B. Foster, a native of Gambia was posted from the colonial office in London to the Accra psychiatric hospital in 1951. He transformed the Asylum into a hospital in conformity with the world wide changes at that time. He initiated changes and training of doctors and nurses who became trainer of trainers. He also arranged for a number of doctors to specialize in the field of psychiatry abroad (Foster, 1962).

The training of Qualified Registered Mental Nursing (Q.R.N.) was started in 1952 by Mrs. Higgison, a British national. The first trained mental nurse, Mr. L.L. Tamakloe joined the training school in 1965. The Ghana Medical School started in 1962 with the inclusion of psychiatric undergraduate training. The appointment of Doctor Asare, a UK trained psychiatrist, coupled with interest from the Head of State in 1983, resulted in the setting

up of a committee to advise the Government on improving psychiatric services in the country and especially in the Accra psychiatric hospital. This was followed by the creation of the Mental Health Unit within the Ministry of Health. It heralded a new era for psychiatry. Training of mental health nurses was enhanced in the early 1990's. Public awareness of mental health issues was intensified. A general drive to reduce the population of the Accra psychiatric hospital from 2,000 to 1,000 was achieved (Asare, 2003).

2.4.1 Contribution of African Traditional Healers to Mental Disorders

The popularity of traditional healers in the treatment of mental illness has been noted since the earliest studies of mental illness in Ghana and continues to the present day. A study of 194 people attending three shrines in the Ashanti region stated that 100 (51.55%) of these were suffering from a mental illness, the majority (32.99%) with depression. Another 14 were diagnosed with somatisation, and 19 with psychotic illness, including 6 with schizophrenia, 4 with acute psychosis and 3 with cannabis-induced psychosis (Read and Doku., 2012). Atindanbila (2000) found that only 2% of the psychiatric patients in the hospital used hospital drugs *solely* for the treatment of their disorders. The remaining patients had visited the traditional healers in addition to the hospital therapies.

According to WHO (2003) the popularity of traditional mental healers is due to the reasons of Confidence in the system that is the explanations offered to the clients as the cause of their illnesses are more acceptable than the allopathic medicine. Some even believe that mental illness can be handled better by traditional healers than modern medicine. Affordability is also one of the reasons accounting to the

popularity of traditional mental healers in the sense that the cost is cheaper and flexible than allopathic medicine. It affords the clients the opportunity to settle their bills when they can afford. More often than not, they pay the bills only when they are fully recovered and can work towards paying the bills. Through oral tradition, some people also do self medication which reduces the cost. The traditional healers are accessible and found in remote areas where hospital facilities cannot be found. Even in such places where facilities are found, they lack the basic drugs and mental health staff to manage them. WHO (2003) statistics have the estimated proportions for the continent as a whole to be 1:200 as compared with 1:100,000 for Western-trained medical doctors and 1:1,000,000 psychiatrists.

Twumasi (1988) classified the African traditional healers of mental illness into the following groups: Herbalists, Spiritualists/Diviners, Faith Healers and Traditional Birth Attendants

Spiritualists/Diviners as explained by Osei (1994) remarked that in the 1930s, the shrines were the first resort of people for who were (presumably) mentally ill, whether trivially or gravely, because the illness is regarded as supernaturally determined and hence outside the province of hospitals. These interveners are priests and priestesses of cults and other fetish agencies. Common examples of such Practitioners in northern Ghana include the `Bagnabas', Balkol-burgas (soothsayers), `Tigare', and Malams'. The Okomfos, another group of spiritualists, dominate in the southern part of Ghana. All groups derive their healing powers

from the Supreme Being, lesser gods or the Ancestors. They use mostly divination in diagnosing the conditions, especially the unexplainable, and assume charismatic roles during healing sessions. They wear particular regalia which serve both for the therapeutic and identification purposes for their clients. Although they attend to all types of illnesses, they deal mostly with the somatoform, dissociative and anxiety disorders.

Faith Healers: According to Osei (1994) the trend of psychiatric clients patronizing both shrines and herbalists started declining in the late 1940s when the indigenous African churches started springing up. This change came from many modernist Africans who considered themselves too sophisticated to visit a shrine and turned to the spiritual churches. Faith healers try to blend traditional values and those of Christianity in their healing rituals. Most of the Syncretic (spiritual) movements partake in this type of healing. Common among these are the Aladura, Nakaba, Mosama Disco Church just to mention a few. They rely on the redramatization of the events of Pentecost which is manifested in possession and "speaking in tongues". In addition to this redramatization, faith healers use Holy Water as well as elements that combine both traditional religion and indigenous practices, such as the singing of hymnals, dancing, practices in the sacrificing of animals, use of natural pharmaceuticals and occult practices. They also rely greatly on certain psychotherapy approaches (described below) to bring relief to their clients. Most of the clients after recovery become members of that church. Another group of faith healers is the "one man" churches or wandering virtuosos whose main practice is

preaching the word of God and healing people of psychological conditions through prayers, songs and other spiritual rituals. According to Twumasi (1988), apart from church services, leaders of these churches also operate healing sessions. Certain days of the week or occasions are set aside for healing purposes. Some also have clinics where both their church members and non-members go for healing.

Traditional Birth Attendants are normally middle aged women (50-70 years) and their skills are acquired either after lengthy experiences with relatives or through spirit possession. The mental problems they handle mostly are puerperal psychoses and postpartum depression. They also do counseling with couples experiencing marital conflicts. They also provide health education to couples on matters related to the proper maternal diet and self-care of women during childbirth (Twumasi, 1988).

2.5 MENTAL HEALTH COMPONENTS IN THE GHANA HEALTH SERVICE

Mental health in Ghana features at two levels - the institutional care and community mental health, popularly known as community psychiatry. The institutional care takes place in public psychiatric hospitals and some private psychiatric hospitals while the community component is practiced at the primary care level, managed by Community Psychiatric Nurses (CPNS)(Standard Treatment Guidelines 2004).

2.5.1 Psychiatric Hospitals

There are currently three psychiatric hospitals in the country namely: (Owiredu *et al* 2012)

1. Accra psychiatric hospital- built in 1906 with a capacity for 800 beds.

2. Ankaful psychiatric Hospital- built in 1965 in the central Region of Ghana. With a capacity for 500 beds.
3. The Pantang hospital was hurriedly commissioned in 1975 to decongest the Accra Psychiatric hospital. The original intention of the then Head of state Dr. Kwame Nkrumah who initiated the building of Ankaful and Pantang was to provide a Pan- African Mental Health Village for Research. It was a grandiose project that would have recruited experts from Africa. Currently the hospital has a capacity for 500 beds.

2.6 ANTIPSYCHOTICS

An antipsychotic (or neuroleptic) is a tranquilizing psychiatric medication primarily used to manage psychosis (including delusions or hallucinations, as well as disordered thought), particularly in schizophrenia and bipolar disorder (Horacek *et al*., 2006).

Antipsychotics are broadly divided into two groups, the conventional or first generation antipsychotics and the atypical or second-generation antipsychotics. The conventional antipsychotics, discovered in the 1950s are classified according to their chemical structure while the atypical antipsychotics are classified according to their pharmacological properties. Horaeck et al (2006) categorised the following as atypical; serotonin-dopamine antagonists, multi-acting receptor-targeted antipsychotics (MARTA, those targeting several systems), and dopamine partial agonists.

Antipsychotics are used in common conditions such as schizophrenia, bipolar disorder and delusional disorder. Antipsychotics might also be used to counter psychosis associated with a wide range of other diagnoses, such as psychotic depression. In addition, "antipsychotics" are increasingly used to treat non-psychotic disorders. For example, they are sometimes used off-label to manage aspects of Tourette syndrome or autism spectrum

disorders (Owiredu *et al*., 2012). They have multiple off-label uses as an augmentation agent (i.e. in addition to another medication), for example in "treatment resistant" depression and obsessive compulsive disorder (OCD). Despite the name, the off-label use of "antipsychotics" is said to involve deploying them as antidepressants, anti-anxiety drugs, mood stabilizers, cognitive enhancers, anti-aggressive, anti-impulsive, anti-suicidal and hypnotic (sleep) medications (Groleger, 2007). Antipsychotics have also been increasingly used off-label in cases of dementia in older people, and for various disorders and difficulties in children and teenagers. A survey of children with pervasive developmental disorder found that 16.5% were taking an antipsychotic drug, most commonly to alleviate mood and behavioural disturbances characterized by irritability, aggression, and agitation (Halliwell B., 2001). Antipsychotics are sometimes used as part of compulsory treatment via inpatient (hospital) commitment or outpatient commitment. This may involve various methods to persuade a person to take the medication, or actual physical force. Administration may rely on an injectable form of the drug rather than tablets. The injection may be of a long-lasting type known as a depot injection, usually applied at the top of the buttocks.

Cipriani (2009), reports that antipsychotics are among the biggest selling and most profitable of all drugs, generating $22 billion in global sales in 2008. By 2003 in the US, an estimated 3.21 million patients received antipsychotics, worth an estimated $2.82 billion. Over two-thirds of prescriptions were for the newer more expensive atypicals, each costing on average $164 compared to $40 for the older types. By 2008, sales in the US reached $14.6 billion, the biggest selling drugs in the US by therapeutic class. The number of prescriptions for children and adolescents doubled to 4.4 million between 2003 and 2006, in part because of increases in diagnoses of bipolar disorder.

2.6.1 SIDE EFFECTS

Antipsychotics are associated with a range of side effects. It is well-recognized that many people stop taking them (around two-thirds even in controlled drug trials) due in part to adverse effects (Bellack, 2006). Extrapyramidal reactions include acute dystonias, akathisia, parkinsonism (rigidity and tremor), tardive dyskinesia, tachycardia, hypotension, impotence, lethargy, seizures, intense dreams or nightmares, and hyperprolactinaernia (Mangrella *et al.*, 1998). Some of the side effects will appear after the drug has been used only for a long time.

The most serious adverse effect associated with long-term antipsychotic use is lowered life expectancy. This has proven most controversial in regard to the use of antipsychotics in dementia in older people, worsened by alleged use to control and sedate rather than necessarily to treat. A 2009 systematic review of studies of schizophrenia also found decreased life expectancy associated with use of antipsychotics and argued that more studies were urgently needed, a call that had already been made when similar results were found in 2006. In "healthy" individuals without psychosis, doses of antipsychotics can produce the so-called "negative symptoms" (e.g. emotional and motivational difficulties) associated with schizophrenia. From a subjective perspective, antipsychotics heavily influence one's perceptions of pleasurable sensations, causing a severe reduction in feelings of desire, motivation, pensive thought, and awe. This does not coincide with the apathy and lack of motivation experienced by the negative symptoms of schizophrenia. Detrimental effects on short term memory, which affect the way one figures and calculates (although this also may be purely subjective), may also be observed on high enough dosages. These are all the reasons why they are thought to affect "creativity". Also, for some individuals with schizophrenia, too much

stress may cause "relapse". The following are details concerning some of the side effects of antipsychotics:

- Antipsychotics, particularly atypicals, appear to cause diabetes mellitus and fatal diabetic ketoacidosis, especially (in US studies) in African Americans (Torrey and Swalwell, 2003); (Koller and Doraiswamy, 2002).
- Antipsychotics may cause pancreatitis (Koller *et al.*, 2003).
- The atypical antipsychotics (especially olanzapine) seem to cause weight gain more commonly than the conventional antipsychotics. The well documented metabolic side effects associated with weight gain include diabetes, which can be life-threatening (Hasnain et al., 2010).
- Antipsychotics increase the likelihood of a fatal heart attack, with the risk of death increasing with dose and the length of time on the drug.
- Clozapine also has a risk of inducing agranulocytosis, a potentially dangerous reduction in the number of white blood cells in the body. Because of this risk, patients prescribed clozapine may need to have regular blood checks to detect the condition early if it does occur, so the patient is in no danger
- One of the more serious of these side effects is tardive dyskinesia, in which the sufferer may show repetitive, involuntary, purposeless movements often of the lips, face, legs, or torso. It is believed that there is a greater risk of developing tardive dyskinesia with the older, conventional antipsychotic drugs, although the newer antipsychotics are now also known to cause this disorder.

A potentially serious side effect of many antipsychotics is that they tend to lower an individual's seizure threshold. Chlorpromazine and clozapine, in particular, have a relatively high seizurogenic potential. Fluphenazine,

haloperidol, pimozide and risperidone exhibit a relatively low risk.

Caution should be exercised in individuals who have a history of seizurogenic conditions such as epilepsy, or brain damage.

- Neuroleptic malignant syndrome, in which the drugs appear to cause the temperature regulation centers to fail, resulting in a medical emergency, as the patient's temperature suddenly increases to dangerous levels.
- Dysphoria
- Sexual dysfunction
- Dystonia - a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures.
- Hyperprolactinaemia - The breasts may enlarge and discharge milk, in both men and women due to abnormally-high levels of prolactin in the blood. Prolactin secretion in the pituitary is normally suppressed by dopamine. Drugs that block the effects of dopamine at the pituitary or deplete dopamine stores in the brain may cause the pituitary to secrete prolactin.
- There is evidence that exposure may cause demyelinating disease in laboratory animals (Konopaske *et al.*, 2008).
- Following controversy over possible increased mortality (death) related to antipsychotics in indivdiuals with dementia, warnings have been added to packaging.

2.6.2 TYPICAL VERSUS ATYPICAL ANTIPSYCHOTICS

While the atypical (second-generation antipsychotics (SGAs)) were marketed as offering greater efficacy in reducing psychotic symptoms while reducing side effects (and extrapyramidal symptoms in particular) than conventional medications, the results showing these effects often

lacked robustness and the assumption was increasingly challenged even as atypical prescriptions were soaring (Geddes *et al.*, 2000). One review concluded there were no differences (Horacek *et al.*, 2006) while another (Leucht *et al.*, 2003) found that atypicals were "only moderately more efficacious" (Horacek *et al.*, 2006). These conclusions were, however, questioned by another review, which found that clozapine, amisulpride, olanzapine and risperidone were more effective (Davis et al., 2003). Clozapine has appeared to be more effective than other atypical antipsychotics (Tuunainen et al., 2000), although it has previously been banned due to its potentially lethal side effects. While controlled clinical trials of atypicals reported that extrapyramidal symptoms occurred in 5-15% of patients, a study of bipolar disorder in a real world clinical setting found a rate of 63%, questioning the generalizability of the trials (Ghaemi et al., 2006). Overall evaluations of the CA TIE study conducted in the US and other studies have led many researchers to question the first-line prescribing of atypicals over conventional, or even to question the distinction between the two classes. The UK government organization NICE recently revised its recommendation favoring atypicals, to advise that the choice should be an individual one based on the particular profiles of the individual drug and on the patient's preferences. The reevaluation of the evidence has not necessarily slowed the bias towards prescribing the atypicals, however.

2.6.3 First Generation Antipsychotics

2.6.3.1 Butyrophenones

- Haloperidol (Haldol, Serenace)
- Droperidol (Droleptan)

2.6.3.2 Phenothiazines

- Chlorpromazine (Thorazine, Largactil)

- Fluphenazine (Prolixin)
- Perphenazine (Trilafon)
- Prochlorperazine (Compazine)
- Thioridazine (Mellaril, Melleril)
- Trifluoperazine (Stelazine)
- Mesoridazine
- Periciazine
- Promazine
- Trifluopromazine (Vesprin)
- Levomepromazine (Nozinan)
- Promethazine (Phenergan) • Pimozide (Orap)

2.6.3.3 Thioxanthenes

- Chlorprothixene (Cloxan, Taractan, Truxal)
- Clopenthixol (Sordinol)
- Flupenthixol (Depixol, Fluanxol)
- Thiothixene (Navane)
- Zuclopenthixol (Cisordinol, Clopixol, Acuphase)

2.6.4 Second Generation Antipsychotics

- Clozapine (Clozaril) - Requires weekly to biweekly complete blood count due to risk of agranulocytosis
- Olanzapine (Zyprexa) -Used to treat psychotic disorders including schizophrenia, acute manic episodes and bipolar disorder.
- Risperidone (Risperdal) - Used off-label to treat Tourette syndrome and anxiety disorder.
- Quetiapine (Seroquel) - Used primarily to treat bipolar disorder and schizophrenia and off-label to treat chronic insomnia and restless legs syndrome; it is a powerful sedative.
- Ziprasidone (Geodon) - Approved in 2006 to treat bipolar disorder.

- Amisulpride (Solian) - Selective dopamine antagonist.
- Asenapine (Saphris) - is a 5-HT_{2A} and D2-receptor antagonist under development for the treatment of schizophrenia and acute mania associated with bipolar disorder.
- Paliperidone (Invega) - Derivative of risperidone
- Iloperidone (Fanapt)
- Zotepine (Nipolept, Losizopilon, Lodopin, Setous) - An atypical antipsychotic indicated for acute and chronic schizophrenia.
- Sertindole (Serdolect)

2.6.5 DRUG ACTION

All antipsychotic drugs tend to block 0_2 receptors in the dopamine pathways of the brain. This means that dopamine released in these pathways has less effect. Excess release of dopamine in the mesolimbic pathway has been linked to psychotic experiences. It is the blockade of dopamine receptors in this pathway that is thought to control psychotic experiences. Conventional antipsychotics are not particularly selective and also block dopamine receptors in the meso cortical pathway, tuberoinfundibular pathway, and the nigrostriatal pathway. Blocking 02 receptors in these other pathways is thought to produce some of the unwanted side effects that the conventional antipsychotics can produce. They were commonly classified on a spectrum of low potency to high potency, where potency referred to the ability of the drug to bind to dopamine receptors, and not to the effectiveness of the drug. High-potency antipsychotics such as haloperidol, in general, have doses of a few milligrams and cause less sleepiness and calming effects than low-potency antipsychotics such as chlorpromazine and thioridazine, which have dosages of several hundred milligrams. The latter have a greater degree of anticholinergic and antihistaminergic activity, which can counteract

dopamine-related side effects (Murphy *et al*, 2006).

Atypical antipsychotic drugs have a similar blocking effect on D2 receptors. Some also block or partially block serotonin receptors (particularly $5HT_{2A}$, C and $5HT_{1A}$ receptors): ranging from risperidone, which acts overwhelmingly on serotonin receptors, to amisulpride, which has no serotonergic activity. The additional effects on serotonin receptors may be the reason why some of them can benefit the "negative symptoms" of schizophrenia (Murphy *et al*., 2006).

2.7 OXIDATIVE STRESS

All aerobic organisms produce free radicals, predominantly superoxide formed as a side product during the reduction of molecular oxygen by mitochondria. The average cell utilizes 10^{13} O_2 per day. It is estimated that 1% of respired molecular oxygen will form O_2^-, thus approximately 10^{11} free radical species are produced by each cell in a day (Xiongwei *et al*., 2004).

An imbalance between cellular pro-oxidants and anti-oxidants can occur during aging as well as during many age-related diseases of the central nervous system (Mariani et al., 2005). This phenomenon is referred to as oxidative stress, and is induced by highly reactive oxygen species (ROS) and reactive nitrogen species (RNS) that possess an unpaired electron (Halliwell., 2001). All macromolecules in the cell are vulnerable to oxidative damage, including lipids, proteins, and nucleic acids (Halliwell., 1999). However, cells are equipped to counteract this oxidative attack with numerous cellular antioxidant defenses such as glutathione (GSH), superoxide dismutases, and catalase. During various disease states, these antioxidant defense systems can be altered leading to progressive oxidative damage and subsequent cell death and/or significant loss of function (Halliwell., 2001). Changes in antioxidant status within specific cells and structures of the brain may be particularly useful in dictating whether oxidative stress is benign or pathological.

2.7.1 Reactive Oxygen Species

Although molecular oxygen is required to sustain life, it can be toxic through the formation of ROS (Rowe., 2009). Approximately 1–3% of oxygen consumed by the body is converted into ROS (Seifried *et al*., 2007). Humans are exposed to many carcinogens, but the most significant may be the reactive species derived from the metabolism of oxygen and nitrogen known as ROS and RNS. On the one hand, the formation of ROS and RNS in the human body can cause oxidative damage to biological macromolecules, especially the plasma membrane which may contribute to the development of cancer, CVD, diabetes and other oxidative stress-mediated dysfunctions (Seihs., 1997). On the other hand, ROS are known mediators of intracellular signalling cascades (Nordberg et al., 2001). Even though ROS are generated under physiological conditions and are involved to some extent as signalling molecules and defence mechanisms as seen in phagocytosis, neutrophil function, macrophages and other cells of immune system,(Halliwell 1996) ROS are a heterogeneous group of molecules that are generated by mature myeloid cells during innate immune responses, and are also implicated in normal intracellular signalling. When phagocytes are activated, they produce ROS in amounts high enough to kill intruding bacteria.(Hole., 2011) Also, shear-stress induced vasorelaxation and excess production of ROS may, on the other hand, lead to oxidative stress, loss of cell function, and ultimately to apoptosis or necrosis (Halliwell., 1996). ROS are produced by oxidative phosphorylation, NADPH, xanthine oxidase, the uncoupling of lipoxygenases, cytochrome P450 monooxygenases, and glucose autoxidation. (Niedowicz and Daleke ., 2005)

Once formed, ROS deplete antioxidant defenses, rendering the affected cells and tissues more susceptible to oxidative damage by reacting with lipids in cellular membranes, nucleotides in DNA, (Ahsan *et al*., 2003) sulphydryl groups in proteins, and cross linking fragmentation of ribonucleoproteins,(Waris G and Alam K., 1998) leading to changes in cellular structure and function.(Phillips *et al*.,

2004) Levels of ROS are under tight control by the protective actions of antioxidant enzymes and nonenzymatic antioxidants in normal and healthy cells.

2.8 OXIDATIVE STRESS AND PSYCHIATRIC DISORDERS

Tsaluchidu *et al*. (2008) reported that there is an association between increased oxidative stress and the majority of psychiatric disorders which correlate with the integration of fatty acids in antioxidants activities, whether from a dietary-habit point of view or from a therapeutic point of view. Oxidative stress mechanisms have been implicated in the pathogenesis of psychiatric disorders (Ng *et al*., 2008). This hypothesis has a theoretical appeal, as the brain is considered particularly vulnerable to oxidative damage for several reasons. These include its comparatively high oxygen utilization and hence generation of free radical by-products, its modest antioxidant defenses, its lipid-rich constitution that provides ready substrates for oxidation, the reducing potential of certain neurotransmitters, and the presence of redox-catalytic metals such as iron and copper (Halliwell, 2006; Valko *et al*., 2007). Additionally, the brain is also susceptible to secondary and self-perpetuating damage from oxidative cellular injury or necrosis, via the neurotoxic effects of released excitatory amines (mainly glutamate) and iron, and the activated inflammatory response (Halliwell, 2006). This intrinsic oxidative vulnerability of the brain, together with the growing evidence for neurodegenerative changes associated with many psychiatric syndromes; suggest that oxidative damage may be a plausible pathogenic cause.

Recently, there has been heightened interest in the role of oxidative stress in neurologic disorders. There is evidence that free radicals play a role in cerebral ischemia-reperfusion, head injury, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Down's syndrome (DS), and AD. The central nervous system (CNS) is especially vulnerable to free radical damage as a result of the brain's high oxygen consumption rate, its abundant lipid content, and the relative paucity of antioxidant enzymes compared with other tissues (Coyle *et al*., 1993). The

appealing feature of the oxidative stress hypothesis for neurodegenerative diseases is that cumulative oxidative damage over time could account for the late life onset and the slowly progressive nature of these disorders (Coyle *et al*., 1993). Increased dopamine turnover, decreased glutathione levels, elevated iron levels, and increased lipid peroxidation in the substantia nigra support the oxidative stress hypothesis in PD (Olanow 1993, Dexter et al.,1999). In ALS, multiple mutations in the copper/zinc (Cu/Zn) superoxide dismutase (SOD-1) gene on chromosome 21 were found in a subset of patients with the familial form of the disease. Thirty (30) transgenic mice overexpressing mutated SOD-1 show only motor neuron degeneration (Gurney *et al* 1994, Wong *et al.,* 1995). Two of the SOD-1 mutant enzymes associated with familial ALS cause the oxidation of a model substrate (spin trap 5,5*-dimethyl-1-pyrroline N-oxide) by H_2O_2 at a higher rate than the wild-type enzyme (Wiedau *et al* 1996). These observations suggest that oxidative reactions catalyzed by mutated SOD-1 can lead to specific neuron degeneration. These findings coupled with studies showing an elevation of iron and selenium levels, and glutathione peroxidase activity in the spinal cord in motor neuron disease patients, strongly suggest that free radical mediated injury of anterior horn cells may be involved in the pathogenesis of ALS (Ince *et al* 1994., Marksbery *et al*., 1995).

2.9 OVERVIEW OF ANTIOXIDANTS

The late 1970s saw the introduction of antioxidant research in the health and clinincal studies with the publication of Cameron and Pauling on vitamins and flavanoids (Cameron., *et al* 1976). Later research found that ascorbic acid (vitamin C) is a potential human cancer protective agent (Rowe., 2009). With many well-known scientists actively researching antioxidants as protecting agents, explanations for the effects of antioxidants on cancer susceptibility and overall health expanded rapidly in subsequent decades with research into mechanisms, molecular targets, and molecular interactions (World Cancer Fund., 1997) In recent

years, many conferences and reviews testify to the increasing interest in the roles of the body's antioxidants system working together in human cells against toxic reactive oxygen species, their relationship with several pathophysiologic processes and their possible therapeutic implications (Mats.,1999)

Antioxidant defense mechanisms involve both enzymatic and nonenzymatic strategies. Common antioxidants include the vitamins A, C, and E, glutathione, and the enzymes superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. Other antioxidants include α-lipoic acid, mixed carotenoids, coenzyme Q_{10}, several bioflavonoids, antioxidant minerals (copper, zinc, manganese, and selenium), and the cofactors (folic acid, vitamins B1, B2, B6, B12). They work in synergy with each other and against different types of free radicals. Vitamin E suppresses the propagation of lipid peroxidation; vitamin C, with vitamin E, inhibits hydroperoxide formation; metal complexing agents, such as penicillamine, bind transition metals involved in some reactions in lipid peroxidation (Maritim *et al* 2002) and inhibit Fenton and Haber-Weiss-type reactions; vitamins A and E scavenge free radicals (Halliwell *et al*.,1990).

Through normal physiological processes, antioxidants affect signal transduction and regulation of proliferation and the immune response. While ROS have been linked to cancer, Psychiatric disorders diabetic complications and Cardio Vascular Diseases, antioxidants have shown promise as a possible therapy for the prevention and treatment of these diseases, especially given the link observed between diets high in fruits and vegetables (and presumably antioxidants) and decreased risks of cancer (Seifried.,2007). Evidence from experimental, epidemiological and clinical studies have proven the utility of antioxidants which might therefore be helpful for treating Psychiatric Conditions.

2.10 TRACE ELEMENT AND PSYCHIATRIC DISORDERS

Neurodegenerative diseases constitute a worldwide health problem. The "bio metals" (e.g., iron, copper, or zinc) are known to play a fundamental role in

numerous essential metabolic processes, thus being considered as essential for life. Metal ion homeostasis is maintained through highly regulated mechanisms of uptake, storage, and secretion (Mills *et al.,* 2010).

A loss or an abnormal metal homeostasis might cause cellular death or severe dysfunction, and it has been recognized as a triggering factor for different neurodegenerative disorders such as Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) diseases as well as amyotrophic lateral sclerosis (ALS) (Liu *et al* 1992 ; Kell, 2010).

Although the etiology of these diseases is still largely unknown, oxidative damage mediated by metals has been thought to be a significant contributor since metals such as iron, aluminum, zinc, and copper have been observed to be deregulated or increased in Alzheimer's Disease brains and therefore prone to generate a pro-oxidative environment (Bica *et al*, 2009 ; Christen, 2000).

Copper (Cu) is required for cellular respiration, iron oxidation, pigment formation, neurotransmitter biosynthesis, antioxidant defense, and connective tissue formation (Pena *et al.* 1999). Furthermore, Cu is essential for the central nervous system development, and therefore disruption of Cu homeostasis during fetal life leads to perinatal mortality, severe growth retardation, and neurodegeneration (Keen *et al.,* 1998). Experiments in mice have revealed that the developmental timing of perinatal Cu deficiency influences the severity of neurological outcome, suggesting a critical period for brain copper acquisition (Prohaska and Brokate., 2002). Acquired copper deficiency in adults results in myelopathy with lower limb spasticity and sensory ataxia due to ascending sensory tract dysfunction and neurodegeneration of the dorsal column (Kumar *et al*., 2004; Prodan *et al*., 2006).

Iron is required as a cofactor in the central nervous system metabolic processes including oxidative phosphorylation, neurotransmitter production, nitric oxide metabolism, and oxygen transport (Ponka., 1999). After uptake, in cells, iron storage is carefully regulated; "free" iron ions do not exist as such. A major

component of this regulation is the protein transferrin, which binds iron ions absorbed from the duodenum and carries it in the blood to cells. (Rousault *et al.*, 2003). In animals, plants, and fungi, iron is often the metal ion incorporated into heme complex. Heme is an essential component of cytochrome proteins which mediate redox reactions and oxygen carrier protein such as haemoglobin, myoglobin and leghmoglobin. Inorganic iron contribute to redox reactions in the iron-sulfur clusters of many enzymes, such as nitrogenase (involved in the synthesis of ammonia from nitrogen and hydrogen) Non-heme iron proteins include the enzymes methane monooxygenase (oxidizes methane to methanol), ribonucleotide reductase (reduce ribose to deoxyribose; DNA biosynthesis), hemerythrins (oxygen transport and fixation in marine invertebrates) and purple acid Phosphatase (Hydrolysis of Phosphate esters). Iron distribution is heavily regulated in mammals, partly because iron ions have a high potential for biological toxicity (Nanami *et al*., 2005)

2.11 TRACE ELEMENT AND OXIDATIVE STRESS

Trace elements and the minerals play a vital role in the body to perform its functions properly. These elements and the minerals should be present in the body in appropriate amounts and must be available for reacting with other elements to form critical molecules as well as to participate in various important chemical reactions.

The ability of iron to accept and donate electrons can lead to the formation of reactive nitrogen and oxygen species which may trigger the oxidative attack of tissue components, therefore contributing to disease.

It is well known that transition metals provoke oxidative stress by generating ROS through the Fenton reaction, thus causing brain lipid peroxidation (Sayre *et al.*, 1997) and protein oxidation (Smith *et al.*, 1997). Interestingly, not only has iron been involved in lipid and protein oxidation but also in DNA damage. It has been shown that iron is able to oxidize DNA bases, and it has been suggested that the

accumulation of this transition metal observed in some neurodegenerative disorders could act by both increasing oxidative genome damage and also preventing its repair (Hegde *et al*., 2010). Both intracellular and extracellular SODs are copper and Zinc-containing enzymes, able to convert superoxide radicals to hydrogen peroxide, which is subsequently removed. Ceruloplasmin also binds copper ions which generate hydroxyl radials (Tietz., 2008). Maganese is a constituent of many important metalloenzymes and also acts as a nonspecific enzyme activator. Mn^{2+} ions will replace Mg^{2+} during the activation of some enzymes. Maganese-dependent SOD is a mitochondrial enzyme and is an important factor in limiting oxygen toxicity. The enzyme catalyses the breakdown of the superoxide radical O^{-2} to H_2O_2 which is then removed by catalase and glutathione peroxidase (Tietz, 2008).

Selenium containing protein in blood plasma, may be a transport protein for the element, and has an antioxidant function. Blood plasma GSHPx-3 (Glutathion Peroxidase) uses the reducing power of glutathione to remove an oxygen atom from hydrogen peroxide and lipid hydroperoxides (Food and Nutrition Board IOM, 2000).

Chapter 3

MATERIALS AND METHODS

3.1 STUDY POPULATION AND SETTINGS

A total of 80 psychiatric patients comprising of 40 newly diagnosed antipsychotic naïve patients and 40 patients on antipsychotic medication visiting the psychiatric department of the Komfo Anokye teaching hospital were recruited for this study. A control group of 20 non psychiatric who had not been associated with any substance abuse, chronic somatic disease, history of psychiatric disorders was involved in this study. Ethical clearance and approval for the study was given by the Committee on Human Research, Publication and Ethics, Kwame Nkrumah University of Science and Technology, School of Medical Sciences & KATH, Kumasi, Ghana.

3.2 INCLUSION CRITERIA

- Newly diagnosed antipsychotic naïve Psychiatric patients
- Patients on any form of antipsychotics.

3.3 EXCLUSION CRITERIA

Control group were not on any medications (antibiotics, Vitamin supplement et cetra). This group were non psychiatric, Tuberculosis free, HIV free and were not presenting any signs of metabolic syndrome.

3.4 BIOCHEMICAL PARAMETERS

Assay parameters include; Trace elements (Copper, Zinc, Selenium, Arsenic, Cadmium, Manganese Lithium and iron), Malondealdehyde (MDA), Vitamain C, and vitamin E. About 8ml of venous blood sample was collected and serum and plasma were extracted. After centrifugation of the serum vacutainer, aliquots were also obtained for Vitamin E analyses. For the vitamin C assay, aliquots of serum were

treated with freshly prepared metaphosphoric acid solution (100 g acid/L). All aliquots were stored at −80°C in cryogenic vials. Serum ascorbic acid levels are stable for up to 2 years if the protein is precipitated with metaphosphoric acid immediately before freezing (Tangney., 1988).

3.5 ASSAY PROCEDURES

3.5.1 *Digestion Protocol for Serum Sample Using Milestone Acid Digestion Microwave* ETOS 900

Two (2g) of serum sample was weighed into a previously acid washed labeled 100ml polytetrafluoroethylene (PTFE) Teflon bombs.

6ml of concentrated nitric acid (HNO_3, 65%), and 1ml of hygrogen peroxide (H_2O_2, 30%) was added to each sample in a fume chamber. The samples were then loaded on the microwave carousel. The vessel caps were secured tightly using a torgue. The complete assembly was microwave irradiated for 25minutes using milestone microwave labstation ETHOS 900, INSTR: MLS-1200 MEGA using the below microwave programme.

Table3-1: INSTRUMENT; MLS-1200 MEGA using the underlisted microwave programme.

Step	Time	Power	Pressure	Temp °C 1	Temp °C 2
1	00:02:00	250	100	400	500
2	00:02:00	0	100	400	500
3	00:06:00	250	100	400	500
4	00:05:00	400	100	400	500
5	00:05:00	650	100	400	500
Vent:00:05:00		Rotorctrl on		Twist on	

Ref: Milestone Acid Digestion Cookbook update 1st January 1996

After digestion the Teflon bombs mounted on the microwave carousel were cooled in a water bath to reduce the internal pressure and allow volatile material to re- stabilize. The digestate was made up to 20ml with double distilled water and assayed for the presence of Zinc (Zn), Lead (Pb) and Copper (Cu), Selenium (Se),Arsenic (As), Iron (Fe), Lithium (Li) Manganese (Mn) using VARIAN AA 240FS- Atomic Absorption Spectrometer in an acetylene- air flame.

Reference standards used for the elements of interest, blanks and duplicates of samples were digested the same conditions as the samples. These served as internal positive controls.

Referece standards (Control Sera) used were from FLUKA ANALYTICAL, Sigma-Aldrich Chemie GmbH, and product of Switzerland.

3.5.2 Quality Control And Quality Assurance

The following Quality Control and Quality Assurance techniques were used during the analysis:

BLANKS: They were to check contamination during sample preparation.

DUPLICATES: They are to check the reproducibility of the method used.

STANDARDS: To check the efficiency of the equipments being used.

3.5.3 Atomic Absorption: Working Conditions.

Table 3-2: Recommended Instrument Parameters

ELEMENT	WAVELENGTH nm	LAMP CURRENT mA	SLIT WIDTH nm	FUEL	SUPPORT
Zn	213.9	5	1.0	ACETYLENE	AIR
Cd	228.8	4	0.5	ACETYLENE	AIR
Cu	324.7	4	0.5	ACETYLENE	AIR
Fe	248.3	5	0.2	ACETYLENE	AIR
Li	670.8	5	1.0	ACETYLENE	AIR
Mn	279.5	5	0.2	ACETYLENE	AIR
Se(By-Hydride)	196.0	10	1.0	ACETYLENE	Argon
As(By-Hydride)	193.7	10	0.5	ACETYLENE	Argon

Ref: VARIAN. Publication No 85- 100009-00 Revised March 1989.

3.6 PRINCIPLES OF ASSAY ATOMIC ADSORPTION SPECTROSCOPY

Atomic Absorption spectrophotometer is an instrument which quantitatively measures the concentrations of element present in a liquid sample. It utilizes the principle that elements in the gaseous phase absorb light at very specific wavelengths. This gives the technique excellent specificity and detection limit. The sample is drawn into a flame where it is ionized in the gaseous phase. Light of a specific wavelength is shown through the flame and the absorption of this light is proportional to the concentration of the element.

Digestion of the samples would be done to get rid of the organic component leaving only the trace elements to be analyzed.

3.7 MALONDIALDEHYDE (MDA)

MDA was determined by the method of Kamal et al., (1989)

Malondialdehyde (MDA) levels were determined by the MDA Thiobarbituric acid (TBA) test which is the colorimetric reaction of MDA and TBA in acid solution. MDA, a secondary product of lipid peroxidation, reacts with thiobarbituric acid (TBA) to generate a red coloured product, which was detected spectrophotometrically at 535 nm. This method is a fast, sensitive and low cost method that can used to indicate the extent of lipid peroxidation in a variety of systems (Shlafer and Shepard, 1984). The protocol used in this study was the (Kamal *et al.*, 1989) modification of the Shlafer and Shepard, (1984) protocol which is as follows: Half a millilitre (0.5 ml) of the patient's serum was treated with 2.5 ml of 20% TCA and then 1 ml of 0.67% of thiobarbituric acid (TBA) added. The mixture was incubated at 100°C for 30 minutes. After cooling, the sample was extracted with 4 ml n-Butanol (product number 334790 supplied by BDH Chemicals Limited), (Poole, England) and centrifuged at 500g for 15 minutes. The absorbance of the extracts was measured at 535 nm and the results were expressed as umol/l, using the extinction coefficient of 1.56×10^{5} L $mmol^{-1}$ cm^{-1}.

3.8 VITAMIN C

Vitamin C was determined by the method of Takahara *et al.,* (1979).

Ascorbic acid in plasma is oxidized by Cu (II) to form dehydroascorbic acid, which reacts with acidic 2, 4 dinitrophenylhydrazine to form a red dihydrazone which is measured at 520 nm. Ascorbic acid should be analyzed immediately or not later than 3 hours if the specimen is refrigerated. To 0.5 ml of plasma 0.5 ml of water and 1 ml of

5% TCA were added, mixed thoroughly and centrifuged at 500g for 15 minutes. To 1 ml of the supernatant, 0.2 ml of DTC (0.4 g thiourea, 0.05 g $CuSO_4.5H_2O$, 3 g 2, 4 dinitrophenylhydrazine in 4.5 mol/L H_2SO_4) was added and incubated at 37°C for 3 hours. Then 1.5 ml of 65% sulphuric acid was added mixed and the solution was allowed to stand at room temperature for another 30 minutes. The colour developed was read at 520 nm. The level of vitamin C was expressed as mg/dl of plasma.

3.9 VITAMIN E

Reversed-phase HPLC (LC-10AD, Shimadzu, HPLC 1991, model-7125, Japan) was used for determination of α-tocopherol in the sera, as described by Bieri et al (1979).

The analytes α-tocopherol was isolated from the serum by liquid-liquid extraction using n-hexane, concentrated by evaporation under nitrogen stream and reconstituted with HPLC-grade ethanol. The reconstituted sample (50 ml) was injected into chromatography on a C_{18} shim pack CLC- ODS (M) column of diameter 4.6 mm (Shimadzu, LC column, 4.6×250 mm), (Japan) with methanol: water (95:5) mobile phase flowing at 1 ml/min, detector set at one attenuation. The column was re-equilibrated with the mobile phase for 5 min before the next injection. Every sample was injected twice to have replicate chromato- graphs. Standard analytes were injected for every 25-30 test samples. Vitamin E (α-tocopherol) was detected spectrophotometrically at 291 nm. Standards (retinol, α-tocopherol, retinol acetate and α-tocopheryl acetate) were purchased from Sigma Chemical Co., USA and solvents (HPLC grade) were obtained from Merck (Darmstadt, Germany).

3.10 ANTHROPOMETRIC VARIABLES

Height to the nearest centimeter without shoes was measured against a wall mounted ruler and weight to the nearest 0.1kg in light clothing on a bathroom scale (Zhongshan Camry Electronics Co. Ltd, Guanzhou China). The body mass index (BMI) was calculated by dividing the weight (kg) over the height squared (m2). Waist circumference to the nearest centimeter was measured with a Gulick II spring-loaded measuring tape (Gay Mill, WI) between the inferior angle of the ribs and the suprailiac crest. Hip circumference was measured as the maximal circumference over the buttocks in metres and the waist to hip ratio (WHR) calculated by dividing the waist circumference (m) by the hip circumference (m)

3.11 STATISTICAL ANALYSIS

Results are presented as Mean ± SD. One way ANOVA was used to compare the means of all continouous variables. The Fischers chi square was used to asses the statistical significance of categorical variable. Odds analysis and confidence intervals of risk factors were done using the Odds ratio test statistic. Pearson correlation test statistic was used to estimate the Pearson Product Moments Correlation among subject. A p-value< 0.05 was considered to be statistically significant. All statistical analyses were performed using GraphPad Prism 5 Project and Microsoft Excel worksheet.

Chapter 4

RESULTS

4.1 GENERAL CHARACTERISTICS

Table 4.1 presents the general characteristics of the study population stratified by treatment. Treatment Naïve Patients had a systolic blood pressure significantly lower (109.3±1.15mmHg) than patients on treatment (117.5±1.49mmHg). Among the three studied population, there was a significant difference in their systolic blood pressure (p=0.0135). Treatment Naïve patients significantly weighed lesser (57.38±1.65kg) than patients on treatment (69.69±1.76kg) and the control group (65.80±2.25kg) (p<0.0001). The mean waist circumference of Treatment naïve patients (80.14±1.55cm) were significantly lower than patients on treatment (93.35±1.97cm) and the control population (93.35±1.97cm) (p<0.0001) likewise the Hip Circumference of treatment naïve patients (93.41±1.19cm) patients on Treatment (106.7±2.35cm) and the control (98.68±2.41cm) (p<0.0001). The mean body mass index of treatment Naïve patient (22.99±0.71kgm^{-2}) was lower compare to the patient s on treatment (26.56±0.69 kgm^{-2}) and control (23.00±1.08 kgm^{-2}) (p=0.0016).

The mean concentrations of copper levels among treatment naïve patient (0.39±0.03mg/l) were significantly lower than patients on treatment (0.44±0.03mg/l) and the control (0.56±0.05mg/l) with a p value of 0.003. The estimated concentration of cadmium was lower in the control group (0.04±0.003mg/l) as compared to the treatment naïve (0.08±0.01mg/l) and patient on treatment (0.09±0.02mg/l). Significantly, cadmium levels in patient on treatment were higher than the control (p=0.0325). The levels of Iron were significantly higher in treatment naïve patient (7.36±0.90mg/l) as compared to the patients on treatment (3.70±0.58mg/l) and the control group (3.58±0.59mg/l) (p=0.0006), likewise the levels of lithium which was significantly higher in Treatment Naïve patients compared to the control (p<0.0001).

Also, estimated concentrations of Arsenic in treatment naïve patients (0.04±0.003mg/l) were significantly higher than the Patients on treatment (0.03±0.003) and the control cases (0.02±0.002mg/l) (p=0.0017).

The mean concentrations of vitamin E in treatment naïve patient (7.67±0.31μg/ml) were significantly lower than that of the patient receiving treatment (9.98±0.26 μg/ml) and the control group (11.98±0.28 μg/ml) (p< 0.0001) but Vitamin C comparatively showed no level of significance although the mean value of the treatment naïve (1.12±0.05mg/dl) were lower than the patient on treatment (1.18±0.07mg/dl) and the control population (1.38±0.08mg/l). Estimated concentrations of Malondialdehyde were significantly higher in treatment naïve patient (0.77±0.02μMol/L) than the patient on treatment (0.69±0.0202μMol/L) and the control (0.66±0.0202μMol/L) (p<0.0001).

Table 4-1: General Characteristics of the study population stratified by Treatment.

Characteristics	Total (n=100)	Treatment Naive (n=40)	On Treatment (n=40)	Control (n=20)	p value
General Characteristics And Anthropometrics					
Age (yrs)	29.49±0.85	30.08±1.57	29.33±1.17	28.65±1.78	0.8232
SBP (mmHg)	113.6±1.28	109.3±1.15*	117.5±2.34	114.5±3.28	0.0135
DBP (mmHg)	74.70±1.114	71.50±2.01	76.75±1.49	77.00±2.18	0.0624
Weight (kg)	63.75±1.20	57.38±1.65*	69.69±1.76	65.80±2.25#	< 0.0001
Height (m)	1.601±1.01	1.59±0.016	1.62±0.015	1.60±0.024	0.2583
HC (cm)	54.29±3.44	93.41±1.19*	106.7±2.35¥	98.68±2.41	< 0.0001
WC (cm)	86.54±1.23	80.14±1.55*	93.35±1.97¥	85.73±2.16	< 0.0001
BMI (kgm^{-2})	71.60±4.14	22.99±0.71*	26.56±0.69	23.00±1.08#	0.0016
WHR	0.87±0.01	0.86±0.014	0.88±0.01	0.87±0.02	0.5491
Trace Element Analysis					
Cu (mg/L)	0.43±0.02	0.39±0.03	0.44±0.03	0.56±0.05#	0.0030
Zn (mg/L)	0.80±0.153	0.62±0.15	1.01±0.35	0.75±0.19	0.5199
Cd (mg/L)	0.08±0.01	0.08±0.01	0.09±0.02	0.04±0.003#	0.0325
Mn (mg/L)	0.08±0.01	0.08±0.01	0.08±0.01	0.05±0.01	0.1386
Fe (mg/l)	5.14±0.48	7.36±0.90*	3.70±0.58	3.58±0.59#	0.0006
Li (mg/L)	0.21±0.02	0.36±0.03*	0.10±0.01	0.14±0.04#	< 0.0001
Se (mg/L)	1.24±0.12	1.11±0.23	1.19±0.16	1.61±0.17	0.2878
As (mg/L)	0.03±0.002	0.04±0.003*	0.03±0.003	0.02±0.002#	0.0017
Analysis Of Oxidative Stress Markers					
Vit C (mg/dL)	1.15±0.04	1.12±0.05	1.18±0.07	1.38±0.08	0.1110
Vit E (μg/ml)	9.45±0.24	7.67±0.31*	9.98±0.26¥	11.98±0.28#	< 0.0001
MDA(μMol/L)	0.71±0.01	0.77±0.02*	0.69±0.02	0.66±0.02#	< 0.0001

Results are presented as mean ± SD. *Defines a significant difference between Treatment-Naïve and Cases On Treatment, ¥ defines significant difference between Cases on treatment and Control and # defines significant difference between control and Treatment naïve cases. P value defines the level of significance among Treatment Naïve, Cases on Treatment and Control (p<0.05). WC = waist circumference, HC = hip cir-cumference, WHR = waist to hip ratio, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, Cu= Copper, Zn=Zinc, Cd=Cadmium, Mn=Manganese, Fe= Iron, Li=Lithium, Se=Selenium, As=Asernic, Vit C= Vitamin C, Vit E= Vitamin E, MDA= malondialdehyde.

Table 4-2: Co-Morbid and Risk factors stratified by treatment among studied population.

Variables	Total (n=80)	On Treatment (n=40)	Treatment Naive (n=40)	OR(95%CI)	P value
Female	45(56.25%)	24(60%)	21(52.5%)	1.4(0.6-3.3)	0.6525
Smokers	9(11.25%)	5(12.5%)	5(10%)	1.3(0.3-5.2)	1.0000
Alcohol	10(12.5%)	5(12.5%)	5(12.5%)	1.0(0.3-3.8)	1.0000
Obesity	11(27.5%)	9(22.5%)	2(22.5%)	5.5 (1.1-27.4)	0.0476
WHR	15(18.75%)	8(20%)	7(17.5%)	1.2(0.4-3.6)	1.0000
SBP	17(21.25%)	12(30%)	5(12.5%)	3.0(0.9-9.5)	0.0993
DBP	13(16.25%)	8(20%)	5(12.5%)	1.6(0.5-5.4)	0.5513
OS	25(31.25%)	18(45.0%)	7(17.5%)	3.9(1.4-10.8)	0.0150

P value defines the level of significance when treatment Naive was compared to Cases on Treatment. WHR = waist to hip ratio, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure OS= Oxidative stress. Obesity is defined as BMI≥30km^{-2} Hypertension is defined as SBP≥140mmHg and DBP≥90mmHg.

4.2 CO-MORBID CONDITIONS

Odds analysis to evaluate the risk of developing certain physical co-morbidities and lifestyle associated with psychiatric disorders based on the treatment are shown in Table 4-2. Patient receiving medication were 5 times at risk of becoming obese (p=0.0476) and 4 times at risk of being oxidatively stressed (0.0150) when compared to treatment naïve patient. Alcoholism, smoking, gender waist to hip circumference, systolic blood pressure and diastolic blood pressure showed no statistical significance between treatment naïve patient and patient on medication.

Table 4-3: Product Moment Correlation Coefficients treatment naïve patients

	Cu	Zn	Cd	Mn	Fe	Li	Se	As	VIT E	VIT C	MDA	AGE	SYST	DIAST	BMI	WHR
Cu		-0.049*	-0.130	-0.169	-0.061	0.286	0.006	-0.130	0.074	**-0.145**	0.023	-0.052	0.094	0.012	0.323	0.241
Zn			**0.318***	0.237	**0.456****	-0.024	**0.946*****	**0.318***	-0.239	**0.255**	0.049	0.162	-0.295	0.124	-0.224	**-0.330***
Cd				**0.906*****	**0.637*****	**0.493*****	0.224	**1.000*****	0.060	0.520***	-0.128	-0.025	-0.095	-0.036	-0.297	-0.281
Mn					**0.520*****	**0.481****	0.146	**0.906*****	0.082	**0.530*****	-0.098	0.058	-0.022	0.016	**-0.325***	**-0.337***
Fe						**0.388***	**0.343***	0.637***	-0.227	**0.157**	0.122	-0.118	0.029	0.105	-0.158	**-0.319***
Li							-0.105	0.493	-0.098	**-0.044**	-0.069	0.080	0.150	0.095	-0.020	0.004
Se								0.224	-0.286	**0.394**	-0.015	0.116	-0.289	0.114	-0.212	-0.265
As									0.060	**0.520*****	-0.128	-0.025	-0.095	-0.036	-0.297	-0.281
VIT E										**0.082**	-0.199	0.006	0.074	-0.081	0.115	-0.109
VIT C											-0.124*	**0.014**	**-0.096**	**-0.014**	**-0.330***	**-0.288**
MDA												-0.010	0.043	0.122	0.202	-0.061
AGE													-0.003	0.172	-0.112	0.012
SBP														**0.648*****	0.152	-0.066
DBP															0.224	-0.216
BMI																0.154
WHR																

Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed), ***Correlation is significant at the 0.001 level (2-tailed). Boldface r = Pearson product moment correlation coefficient with a medium size (0.30 ≤ r ≥ 0.50) effect: boldface and underlined r= Pearson product moment correlation coefficient with a large size (r > 0.50) effect, DIS = dissatisfaction.

WHR = waist to hip ratio, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, Cu= Copper, Zn=Zinc, Cd=Cadmium, Mn=Manganese, Fe= Iron, Li=Lithium, Se=Selenium, As=Arsenic, Vit C= Vitamin C, Vit E= Vitamin E, MDA= malondialdehyde.

Table 4-4: Pearson Product Moment Correlation Coefficients of patients on treatment

	Cu	Zn	Cd	Mn	Fe	Li	Se	As	VIT E	VIT C	MDA	AGE	SYST	DIAST	BMI	WHR
Cu																
Zn	-0.115															
Cd	0.236	0.164														
Mn	0.096	0.326*	**0.425****													
Fe	0.057	**0.621*****	**0.456****	**0.501****												
Li	0.306	0.046	**0.352***	0.180	**0.586*****											
Se	-0.162	**0.453****	-0.205	-0.059	-0.015	-0.254										
As	-0.040	**0.720*****	**0.369***	**0.562*****	**0.880*****	**0.325***	0.219									
VIT E	0.238	-0.272	0.051	-0.137	-0.284	-0.053	-0.020	-0.305								
VIT C	0.129	0.198	0.034	0.013	0.191	0.154	0.191**	0.126	-0.294							
MDA	0.203	0.021	-0.255	-0.117	0.250	0.268	-0.100	0.153	-0.192	0.125						
AGE	0.138	-0.206	-0.019	-0.119	-0.123	0.001	-0.180	-0.226	-0.027	-0.179	0.104					
SBP	0.119	0.010	-0.022	-0.078	-0.023	0.142	0.020	-0.057	0.026	0.048	-0.070	0.281				
DBP	-0.293	0.224	-0.023	0.017	0.060	0.126	0.305	0.091	**-0.314***	0.250	-0.154	-0.028	**0.512*****			
BMI	0.016	-0.100	0.050	-0.108	-0.068	0.177	-0.194	-0.245	0.117	-0.253	0.034	0.265	-0.005	-0.198		
WHR	0.082	-0.167	-0.158	-0.086	0.045	0.155	**-0.377***	-0.105	0.018	-0.079	0.116	0.168	-0.152	-0.286	0.158	

Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed), ***Correlation is significant at the 0.001 level (2-tailed). Boldface r = Pearson product moment correlation coefficient with a medium size (0.30 ≤ r ≥ 0.50) effect: boldface and underlined r= Pearson product moment correlation coefficient with a large size (r > 0.50) effect, DIS = dissatisfaction.

WHR = waist to hip ratio, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, Cu= Copper, Zn=Zinc, Cd=Cadmium, Mn=Manganese, Fe= Iron, Li=Lithium, Se=Selenium, As=Arsenic, Vit C= Vitamin C, Vit E= Vitamin E, MDA= malondialdehyde.

4.3 CORRELATION BETWEEN TRACE ELEMENT AND OXIDATIVE STRESS

Results for the Pearson Product Moments Correlation are shown in Table 4-3 (treatment naïve patients) and 4-4 (patients on treatment). For the treatment naïve patients, copper levels correlated negatively to a small size effect with zinc levels. No correlations with the other trace elements, oxidative stress markers and the anthropometric measures were however observed. In contrast, no correlation between copper and zinc was observed in patients on treatment. With the exception of lithium and manganese, zinc correlated positively with all other trace element to a medium size (cadmium, iron, arsenic) and large size effect (selenium). No such correlations were observed for the oxidative stress marker, but among the anthropometric measures, waist-to-hip ratio showed a negative (to a medium size effect) correlation with zinc levels. For patients on treatment, positive correlations were also observed between zinc levels and other trace elements, with the exception of lithium and cadmium. Cadmium levels in treatment naïve patients correlated positively with all trace elements with the exception of selenium, to a large size effect (manganese, iron, arsenic) and medium size effect (lithium). Among the oxidative stress markers, cadmium correlated positively with a large size effect with vitamin C levels. A similar trend was observed in trace element levels of patients receiving treatment. No correlation was however observed in both oxidative stress markers and anthropometric measures. Levels of manganese in treatment naïve patients correlated positively with cadmium and lithium with a medium size effect, and iron and arsenic with a large size effect. Manganese also correlated positively with vitamin C levels with a large size effect. Moreover, BMI and waist-to-hip ratio showed a negative correlation (medium size effect) with manganese. Manganese levels of patients on treatment on the other hand only correlated positively with zinc and cadmium (medium size effect) as well as iron and arsenic (large size effect). For lithium,

treatment naïve patients showed a positive correlation with cadmium, manganese and iron to a medium size effect, whereas patients on treatment showed positive correlations with cadmium (medium size effect) and iron (large size effect). Selenium levels of treatment naïve patients did not show any correlations with the trace elements, except for zinc (large size effect) and iron (medium size effect). Similarly, patients on treatment showed a positive correlation with zinc to a medium size effect. Also patient receiving medication showed a medium size effect with with vitamin C. However, waist-to-hip ratio levels in this group of patients showed a negative medium size effect correlation. Vitamin E levels of treatment naïve patients showed no observed correlations with neither the trace elements nor anthropometric measures. A similar observation was made for patients on treatment, with the exception of waist-to-hip ratio which showed a negative correlation. MDA as an oxidative stress marker showed a negative correlation with vitamin C for treatment naïve patients but did not show any correlations as far as those on treatment were concerned.

Table 4-5: Psychiatric Disorders stratified by treatment among study population

Variable	Total (n=80)	Treatment Naive (n=40)	On Treatment (n=40)	P value
An Dis.	3(3.8%)	2(5%)	1(2.5%)	1.0000
Bip Dis.	16(20%)	12(30%)	4(10%)	0.0488
Uni Dis	3(3.8%)	2(5%)	1(2.5%)	0.6104
Schi Dis	38(47.5%)	14(35%)	24(60%)	0.0432
APsy Dis	8(10%)	2(5%)	7(15%)	0.1543
Other Disorders	12(15%)	7(15%)	5(5%)	0.7555

An Dis.=Anxiety Disorders, Bip Dis. =Bipolar Disorders, Uni Dis= Unipolar Disorders, Schi Dis= Schizophrenic Disorders, Del= Delerium, APsy Dis= Acute Psychotic Disorders, Other Disorders Include Hallucination, Cerebral Palsy and Dementia. P value defines the level of significance when treatment Naive was compared to Cases on Treatment.

Table 4-6: Univariate analysis of Schizophrenic Disorders Stratified by Population.

Characteristics	Total (n=38)	Treatment Naïve (n=14)	Cases On Treatment (n=24)	P value
Gender				
Male	17(44.7%)	7(50%)	10(41.7%)	0.7396
Female	21(55.3%)	7(50)	14(58.3%)	0.7396
Marital Status				
Married	12(31.6%)	8(57.5%)	4(16.7%)	0.0144
Single	26(68.4%)	6(42.5%)	20(83.3%)	0.0148
Educational Status				
Secondary	20(52.6%)	6(42.8%)	15(62.5%)	0.0362
Basic	12(31.6%)	6(42.8%)	7(29.2%)	0.4864
None	6(15.8%)	2(14.4%)	2(8.3%)	0.6161
Occupation				
Self Employed	13(34.2%)	4(28.6%)	9(37.5%)	0.7222
Unemployed	3(7.9%)	0(0.0%)	3(12.5%)	0.2831
Non Governmental work	2(5.2%)	0(0.0%)	2(8.3%)	0.522
Farming	1(2.6%)	0(0.0%)	1(4.2%)	1.000
Student	19(50%)	10(78.6%)	9(37.5%)	0.0205

4.4 PSYCHIATRIC DISORDERS AND ITS DISTRIBUTION

Psychiatric disorders among the studied population stratified by treatment are shown in Table 4-5. Bipolar disorders among treatment naïve 12(30%) was significantly more than the patients receiving treatment 4(10%) (p=0.0488). Diagnosis of schizophrenic disorders were significantly more in patients receiving treatment 24(60%) as compared to Treatment naïve patient 14(35%) (p=0.0432).

Treatment naïve married cases were significantly (p=0.0144) showing a higher schizophrenic disorders compared with patients on medication Table 4-6, whereas patient receiving treatment presented significant (p=0.0148) higher levels of schizophrenic disorders compared to treatment naïve patient. Treatment naïve student patients 10(78.6%) were significantly presenting schizophrenic disorders as against patients receiving medication 9(37.5%) p=0.0205. Marital status and educational levels showed no significant changes between treatment naïve cases and patients receiving medication.

Table 4-7 shows the stratification of the results of patient on typical treatment, atypical treatment and a combined therapy of typical and atypical treatment. The mean age, weight, height, waist to hip circumference, Systolic blood pressure, Diastolic blood pressure and body mass index in the typical treatment group were not significantly different from that in the atypical treatment and the combined therapy of typical and atypical group (p>0.05). The mean Hip circumference of the typical group (103.9±2.04cm) were significantly higher than that of the atypical treatment group (95.84±2.29cm) and the group receiving combined therapy of typical and atypical medication (98.86±4.51cm) (p=0.0484). Also the Waist circumference of the typical antipsychotic treatment group (90.07±1.95cm) were significantly higher as compared to the group receiving atypical medication (83.14±2.31cm) and the other group receiving combined therapy of typical and atypical medication (85.58±4.23cm)

(p=0.0476). Vitamin C showed significant lower levels in typical antipsychotic medication group (1.03±0.05md/dl) as compared to patients receiving atypical antipsychotics (1.24±0.07mg/dl) and the patient receiving combined therapy of typical and Atypical medication (1.25±0.15mg/dl) (p=0.0477).

Table 4-7: General characteristics of the study population stratified by type of medication.

Variable	Typical (n=22)	Atypical (n=9)	(Atypical & Typical) (n=9)	P value
General Characteristics And Anthropometrics				
Age(years)	28.03±1.24	31.67±1.91	29.92±1.89	0.2364
SBP(mmHg)	112.7±1.14	112.9±3.32	116.2±1.80	0.6720
DBP(mmHg)	74.05±1.75	73.33±2.55	76.15±1.80	0.7627
WEIGHT(kg)	70.57±2.70	73.33±2.55	76.15±1.80	0.4511
HEIGHT(m)	1.62±0.02	1.59±0.02	1.55±0.03	0.0559
HC(cm)	103.9±2.04*	95.84±2.29	98.86±4.51	0.0484
WC(cm)	90.07±1.95*	83.14±2.31	85.58±4.23	0.0476
BMI(kgm^{-2})	25.61±0.90	29.43±3.21	29.14±3.51	0.3019
WHR	0.87±0.01	0.87±0.02	0.87±0.02	0.9958
Trace Element				
CU(mg/L)	0.40±0.03	0.39±0.03	0.45±0.05	0.6252
ZN(mg/L)	0.79±0.36	0.74±0.20	1.06±0.30	0.8399
Cd(mg/L)	0.07±0.01	0.09±0.01	0.12±0.04	0.2608
Mn(mg/L)	0.08±0.01	0.08±0.01	0.06±0.01	0.6150
Fe(mg/L)	4.63±0.66	6.08±0.70	6.82±2.61	0.3270
Li(mg/L)	0.21±0.04	0.29±0.03	0.17±0.05	0.1464
Se(mg/L)	0.89±0.17	1.33±0.27	1.49±0.34	0.2124
As(mg/L)	0.03±0.004	0.04±0.002	0.03±0.004	0.1926
Oxidative Stress Markers				
VitC(mg/dl)	1.03±0.05*	1.24±0.07	1.25±0.15	0.0477
VitE(µg/ml)	8.83±0.32	8.47±0.41	9.59±0.68	0.2873
MDA(µMol/L)	0.74±0.03	0.74±0.03	0.74±0.06	0.9978

Results are presented as mean ± SD. *Defines the significant difference between Typical Drugs and Atypical Drugs. P value defines the level of significance among Treatment Naïve, Cases on Treatment and Control. WC = waist circumference, HC = hip cir-cumference, WHR = waist to hip ratio, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, Cu= Copper, Zn=Zinc, Cd=Cadmium, Mn=Manganese, Fe= Iron, Li=Lithium, Se=Selenium, As=Asernic, Vit C= Vitamin C, Vit E= Vitamin E, MDA= malondialdehyde.

Chapter 5

DISCUSSION

5.1 GENERAL CHARACTERISTICS OF PSYCHIATRIC DISORDERS

Anthropometrics of study sample were taken to establish the effect of antipsychotics on some parameters such as blood pressure, body mass index and waist to hip ratio. The study revealed that treatment Naïve Patients had a systolic blood pressure significantly lower (109.3±1.15mmHg) than patients on treatment (117.5±1.49mmHg). Reid *et al* 2007 in a research to determine Weight and blood pressure changes after switching second-generation antipsychotics in a population of veterans with schizophrenia-related disorders reported a significantly increased systolic blood pressure in patients taking second generation antipsychotic, this he attributed to the side effect of the antipsychotic therapy. The weight, BMI, Hip circumference, and waist circumference of patients on antipsychotic treatment was significantly higher than treatment naïve patients. Studies indicate that there is a high risk of metabolic syndrome in patients with Psychiatric disorders independent of medication (owiredu *et al*, 2012). Thakore, et al 2002 in a study of larger population found significant differences between drug-naive patients with schizophrenia and matched controls, and found that patients receiving antipsychotic drugs experience substantial deposition of both subcutaneous and intra-abdominal fat. People with metabolic syndrome are three times more likely to suffer a cardiovascular accident or myocardial infarction and have a five times greater risk of developing type 2 diabetes mellitus (Barnett *et al* 2007). The International Diabetes Federation (IDF) and the The *Maudsley Prescribing Guidelines* provide guidance on monitoring parameters of patients on antipsychotics which include weight-including waist circumference as a marker of obesity, Hip circumference and body mass index at baseline, frequently for 3 months then yearly. Patients on clozapine, olanzapine, quetiapine should frequently measure

their weight and body mass index for 3 months, then 3 times monthly for first year, then yearly.

5.2 TRACE ELEMENT DYSMETABOLISM IN PSYCHIATRY

A number of essential trace elements play a major role in various metabolic pathways. Selenium (Se), manganese (Mn), copper (Cu), zinc (Zn), and iron (Fe) are essential trace elements that have been studied in many diseases, including autoimmune, neurological, and psychiatric disorders. These elements and the minerals should be present in the body in appropriate amounts and must be available for reacting with other elements to form critical molecules as well as to participate in various important chemical reactions.

A loss or an abnormal metal metabolism might cause cellular death or severe dysfunction, and it has been recognized as a triggering factor for different neurodegenerative disorders such as Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) diseases as well as amyotrophic lateral sclerosis (ALS) (Liu et al 1992 ; Kell, 2010). The metabolism of trace element among the studied population was estimated and their result presented as mean ± SEM. The mean concentrations of copper levels among treatment naïve patient (0.39±0.03mg/l) were significantly lower than patients on treatment (0.44±0.03mg/l) and the control (0.56±0.05mg/l). Ralph et al 2001 reported that copper is absorbed, transported, distributed, stored, and excreted in the body according to complex homeostatic processes which is defective in treatment naïve patients. Estimated levels of cadmium among the control were also significantly lower compared to the treatment naïve psychiatric patient which was in tandem with Cowen's work on bipolar disorders stating the median serum levels of cadmium to be significantly higher in bipolar patients than controls, at 3.00 versus 2.20 μg/dl, and 0.39 versus 0.10 μg/l, respectively. Concentrations of iron, Lithium and arsenic were significantly higher in treatment naïve psychiatric patients than patient receiving antipsychotic medication. Initial guidelines recommend lithium or valproate as

first-line treatments for mania, and antipsychotic agents only as 'adjuncts' for agitation, dangerous behaviour or psychosis. However, in recent routine practice, antipsychotic drugs are often prescribed. The effectiveness of these agents in mania has been established by several studies. Newer atypical compounds demonstrate antimanic efficacy with a reduced incidence of neurological side-effects hence the significant lower levels in patients receiving treatment.

5.3 DETERMINATION OF OXIDATIVE STRESS IN PSYCHIATRIC PATIENTS.

Numerous physiological and pathological processes such as ageing, excessive caloric intake, infections, inflammatory disorders, environmental toxins, pharmacological treatments, emotional or psychological stress, ionizing radiation, cigarette smoke and alcohol increase the bodily concentration of oxidizing substances, known as reactive oxygen species (ROS) or, more commonly, free radicals. These are chemical species which are highly reactive owing to the presence of free unpaired electrons. An increase in free radicals compromises the delicate homeostatic mechanisms which involve neurotransmitters, hormones, oxidizing substances and numerous other mediators (Hadjigeorg., 2008). Owing to their structure, which is rich in double bonds, polyunsaturated fatty acids (PUFAs) render cellular membranes vulnerable to damage from free radicals, causing peroxidation? The damage induced by lipid peroxidation renders the cell unstable, and therefore compromises fluidity, permeability, signal transduction and causes receptor, mitochondrial DNA and nuclear alterations (Hadjigeorg., 2008).

5.3.1 Oxidative stress and Psychiatric Disorders

In this study, vitamin E which is a lipid soluble vitamin showed a significantly increased level in treatment naïve patient (7.67±0.31 μg/ml) compared to patient receiving medication (9.98±0.26 μg/ml) and the control group (11.98±0.28 μg/ml). Comparatively Vitamin C showed no level of significance although the mean value of the treatment naïve (1.12±0.05mg/dl) was lower than the patient on treatment

(1.18±0.07mg/dl) and the control population (1.38±0.08mg/dl). Estimated concentrations of Malondialdehyde were significantly higher in treatment naïve patient (0.77±0.02μMol/L) than the patient on treatment (0.69±0.02μMol/L) and the control (0.66±0.02μMol/L). Adler *et al* (1998) reported that Haloperidol and related antipsychotic drugs can cause a movement disorder called tardive dyskinesia (Symptoms of tardive dyskinesia include repetitive and involuntary movements, most often of the facial muscles and tongue (such as lip smacking), although any muscle in the body can be affected (e.g., moving legs back and forth). Symptoms may be mild or severe and can interfere with eating and walking). Adher *et al* (1998) continue to report that several double-blind studies suggest that vitamin E is beneficial for treatment of tardive dyskinesia. Hence Vitamin E forms major component of some antipsychotics such as Trihexyphenidyl (Artane, Trihexy) which is further expressed in significant high levels in serum of patients on antipsychotic medication. One important finding of this study was that plasma levels of membrane lipid peroxidation products (MDA) were found to be elevated significantly in treatment naïve patients compared to patients receiving medication. It is an established fact, that oxidative stress within the CNS is reflected in plasma (Arvindakshan *et al.*, 2003) and hence patients who are not being managed with antipsychotics will have higher levels of membrane lipid peroxidation products.

Oxidative stress from free radicals is one of the factors which contribute to an increase in the speed of the cell cycle and consequent premature cell death, leading to many degenerative illnesses in the central nervous system, as well as psychiatric disturbances. Our study indicates that there is an association between increased oxidative stress and the generalized psychiatric disorders. Evidentially the highest degree of oxidative damage usually occurs in organs like brain, heart and skeleton muscle since these organs are composed primarily of post- mitotic cells (Sohal and Weindruch 1996). The central nervous system shows increased susceptibility to oxidative stress because of its high consumption rate (20% of the total oxygen

inhaled by the body) that accounts for the increased generation of oxygen free radicals and reactive oxygen substrates. Since all the cells and tissues of our body are also equipped with anti oxidative enzymes like super oxide dismutase (SOD), glutathione peroxidase (GSH-PX),glutathione reductase (GRd) and substances like reduced glutathione (GSH), they dispose the free radicals as and when they are generated thereby protecting the cells and tissues from the oxidative attack (khanna *et al.,* 2012). Normally a balance is maintained between the oxidative attack of the free radicals and the antioxidative defense system prevailing in the cells and tissues of body but when the balance is tilted more towards the generation of free radicals, then degenerative changes cause many degenerative diseases. Brain has a low level of antioxidative defense system as the concentration of various antioxidative enzymes like SOD, GSH-PX, GRd and catalase is low in brain (Savolainen 1978). In addition brain has a high iron and ascorbate content in certain regions, which provide favorable environment for generation of oxygen free radicals. Brain is also enriched with polyunsaturated fatty acids that render neuronal cells easily vulnerable to oxidative attack. The interplay of all these factors contributes to enhance the oxidative stress among psychiatric patients (Zhang *et al* 1993).

5.4 CO-MORBIDITY AND PSYCHIATRIC DISORDERS

Psychiatric disorders are increasing in prevalence and are associated with a variety of health complications. Multiple studies have shown that people with severe mental illness represent a vulnerable population—at risk for various medical conditions (Koran *et al* 2002 ; Eilley *et al* 2006), and among whom mortality rates are very high (Brown *et al* 2000) or life expectancy is much lower than that seen in the general population. As health problems, overweight and obesity are common in the general population and causes for growing concern in clinic populations, especially those patients with severe mental illness. Several recent studies indicate

that patients with persistent or severe psychiatric disorders are more likely than the general population to be obese (Pickering *et al* 2007). This study revealed that patient receiving medication compared to treatment naïve patient, were 5 times at risk of becoming obese (p=0.0476) and 4 times at risk of being oxidatively stressed (p=0.0150). This confirms a study conducted by Owiredu *et al* 2012. There are also various articles on research into the risk of depression and other psychiatric disorders, with obese individuals as the index population (nyike *et al* 2003; Amann *et al* 2009); these report a weak correlation between obesity and the risk of depression. Previous studies indicate that patients with persistent or severe mental illness are at increased risk for obesity because of the illness itself as well as its treatment. Alcoholism, smoking, gender waist to hip circumference, systolic blood pressure and diastolic blood pressure showed no statistical significance between treatment naïve patient and patient on medication.

5.5 CORRELATION BETWEEN TRACE ELEMENT AND OXIDATIVE STRESS.

Increasing evidence about the effects of trace elements on brain and behavioral functioning is continually investigated by researchers. Zinc, copper, and magnesium play an important modulatory role in controlling a subtype of glutamate receptor (NMDA receptor), (Sandstead *et al.,* 2000), glutamate being the primary transmitter for most excitatory neurons in the cerebral cortex. This N-methyl-D-aspartate (NMDA) receptor has been implicated in various forms of cortical functioning; (Martin *et al.,* 2000) therefore it appears that decreased levels of these nutrients may produce abnormal NMDA activity and subsequent abnormal behavior. Given the accumulating evidence from Position Emission Tomography and functional Magnetic Resonance Imaging imaging studies showing that schizophrenia and affective disorders are associated with abnormal cortical activity, (Elkashef *et al.,* 2000) it is logical to state that such conditions could result, at least in part, from abnormalities in the nutritional status of neurons.

Comparison studies have shown that 26 medication-free schizophrenics were found to have significantly low serum iron, (Weiser., *et al* 1994).

This study revealed that in treatment naïve patients, copper levels correlated negatively to a small size effect with zinc levels which we attributed to inverse relationship between Zn^{2+} and Cu^{2+} concentration. No correlations with the other trace elements, oxidative stress markers and the anthropometric measures were however observed with copper concentrations. In contrast, no correlation between copper and zinc was observed in patients on treatment a finding from this research which needs further investigation.

Zinc correlated positively to a medium size effect with cadmium, iron, arsenic and large size effect with selenium. With the exception of lithium and manganese, zinc correlated positively with all other trace element to a medium size (cadmium, iron, arsenic) and large size effect (selenium). No such correlations were observed for the oxidative stress marker, but among the anthropometric measures, waist-to-hip ratio showed a negative (to a medium size effect) correlation with zinc levels which is consistent with Garcia *et al* (2012) who made the findings that in women living in rural Mexico, zinc concentrations were positively associated with measures of obesity and adiposity. Zinc again correlated positively with other trace elements, with the exception of lithium and cadmium of patients receiving medication.

As cadmium increased in treatment naïve patient; manganese, iron, arsenic and lithium also increased. A similar trend of cadmium metabolism was observed in trace element levels of patients receiving treatment. No correlation was however observed in both oxidative stress markers and anthropometric measures. Cadmium is closely associated with many developmental, behavioral and mental disorders. Cadmium is somewhat antagonist to iron and manganese which is one reason why these minerals are in bio unavailable state, as they counter cadmium toxicity strongly hence the body may seek to protect itself from cadmium by accumulating bio unavailable iron and manganese (Willson., 2012). This explains the positive correlation between cadmium, iron and manganese in treatment naïve

patient. MDA as an oxidative stress marker showed a negative correlation with vitamin C for treatment naïve patients but did not show any correlations as far as those on treatment were concerned. Selenium performs antioxidative functions through proteins in which they are incorporated (El-Bayoumy 2001). Selenium is a component of about 25 enzymes including the GSH-Px family, thioredoxin reductases and selenoprotein P which provide antioxidant protection against ROS-driven cancer initiation and promotion, as well as some others (Zachara *et al*., 2006; Brozmanova *et al*., 2010). In this research, Selenium levels of treatment naïve patients did not show any correlations with the trace elements, except for zinc in large size effect and iron medium size effect but in patient receiving medication, selenium levels correlated positively with vitamin C in a medium size effect.

5.5 TYPICAL, ATYPICAL ANTIPSYCHOTICS AND PSYCHIATRY

The typical antipsychotics (first-generation antipsychotics (FGAs)) are still widely available and are effective at treating positive symptoms of psychosis, such as hallucinations and delusions. FGAs do not, however, adequately alleviate many other common and important aspects of psychotic illness, such as negative symptoms (e.g., withdrawal, apathy, poverty of speech), cognitive impairment, and affective symptoms. In addition, all FGAs can produce significant extrapyramidal side effects at clinically effective doses. These side effects, which include dystonic reactions, drug-induced Parkinsonism, akathisia, and tardive dyskinesia, can make treatment intolerable for some people, leading to subjective distress, diminished function, stigma, and nonadherence (American Diabetes association). This explains why vitamin C levels were significantly reduced in patients receiving FGAs as compared to patient on Atypical (second generation antipsychotics (SGAs)). With the introduction of the second-generation antipsychotics (SGAs) over the last decade, the use of these medications has soared. Although the SGAs have many notable benefits compared with their earlier counterparts, their use has been associated with reports of dramatic weight

gain, diabetes (even acute metabolic decompensation, e.g., diabetic ketoacidosis [DKA]), and an atherogenic lipid profile (increased LDL cholesterol and triglyceride levels and decreased HDL cholesterol) (American Diabetes association). Contrary to these findings and a study conducted by owiredu et al on prevalence of metabolic syndrome in psychiatric patient, hip circumference and waist circumference were significantly higher in patients receiving FGAs as compared to SGAs medications.

Chapter 6

CONCLUSION AND RECOMMENDATION

The present investigation found that psychiatric individuals had significant disturbances in metabolism and homeostasis of trace element levels (Cu, Zn, Fe, Se, Cd, As, Li, and Mn), lipid peroxidation and antioxidant levels.

The study revealed that iron, lithium and arsenic levels were significantly higher in treatment naïve patient as compared to patient on antipsychotic medication and the control. The Department of Laboratory Medicine, University of Washington, Seattle report that increased iron in the brain, which is rich in oxygen and fatty acids, provides an ideal environment for oxidative stress and possible irreparable tissue damage. If, indeed, iron and/or oxidative processes are involved in the pathogenesis of neurodegenerative disorders, approaches such as iron chelation therapy and antioxidant supplements might help slow the degenerative processes or ameliorate brain tissue injury.

It is clear from this study that during the progression of psychiatric disorders, there is a concomitant induction of cellular oxidative stress characterized by; an increase in Malondialdehyde (MDA), a product from lipid peroxidation and reduced scavenging activities of vitamin C and E. This demonstrates a derangement in the antioxidant system of treatment naïve psychiatric patients. It is likely from this study that adverse effect of ROS can be alleviated in psychiatric patients by administration of Antioxidants as a combination therapy with Antipsychotics which at cellular level will alleviate the effect of ROS and lead to the proper management of psychiatric disorders.

These are just a few ways in which micronutrients can play a beneficial role in the treatment of several psychiatric illnesses. As researchers continue to investigate the effect of trace element in psychiatric disorders, more and more information will be readily available to managers of psychotic disorders and It therapy. It is further recommended that studies are done to establish the relationship between Selenium

Copper, Zinc and Cadmium among psychiatric patients in the country. This study suggested an association between antipsychotics and obesity. This potential relationship is of considerable clinical concern because obesity is an important risk factor for Cardiovascular Disease, and the relative risk of Cardiovascular Disease mortality is significantly greater in people with psychiatric disorders than in the general population. Despite the adverse effects of antipsychotics, a number of factors should be considered when choosing among the antipsychotic medications. These include the nature of the patient's psychiatric condition, specific target signs and symptoms, past history of drug response (both therapeutic and adverse), patient preference, history of treatment adherence, medication effectiveness, psychiatric and medical comorbidities, availability of appropriate formulations (e.g., fast-dissolving oral, short- or long-acting intramuscular), need for special monitoring, and cost of and access to medications. Nonetheless, the risks of obesity have considerable clinical implications in this patient population and should also influence drug choice.

Although several studies have shown that drug abuse is a contributing factor to psychortic disorders. This study however could not establish that fact, hence further studies in this area is welcomed.

REFERENCE

Adler LA., Peselow E., Rotrosen J. (1993). Vitamin E treatment of tardive dyskinesia. *Am J Psychiatry*; 150:1405–7.

Adler LA., Edson R., Lavori P. (1998). Long-term treatment effects of vitamin E for tardive dyskinesia. *Biol Psychiatry*; 43:868–72

Ahsan H., Ali A., Ali R. (2003); Oxygen free radicals and systemic autoimmunity. *Clin Exp Immunology*. 31:398–404.

Akiskal HS, Benazzi F (2006). "The DSM-IV and ICD-10 categories of recurrent [major] depressive and bipolarII disorders: evidence that they lie on a dimensional spectrum". *J Affect Disorder* 92 (1): 45-54.

Alonso J., Angermeyer MC., Bernert S. (2004). "Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project". *Acta Psychiatr Scand Suppl* 109 (420): 21–7.

American Diabetes Association, Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes.

American Psychological Association, Division 12, http://www.apa.org/divisions/div12

Arvindakshan M., Sitasawad S., Debsikdar V. (2003), Essential polyunsaturated fatty acid and lipid peroxide levels in never medicated and medicated schizophrenia patients. *Biol Psychiatry*; 53:56–64.

Asare G, A., Nani A. (2010) Serum Levels of Cu, Se, and Zn in Adult Rural/Urban Residents in Ghana: Paradigm Shift, *Bio Trace Element Reserve*, 137**:** 139-149

Amann B, Mergl R, Torrent C, Perugi G, Padberg F, El-Gjamal N, (2009). Abnormal temperament in patients with morbid obesity seeking surgical treatment. *J Affect Disord*.; 118:155-60.

Barnett AH., Mackin P., Chaudhry I., Farooqi A., Gadsby R., Heald A. (2007) Minimising metabolic and cardiovascular risk in schizophrenia: diabetes, obesity and dyslipidaemia. *J Psychopharmacol*; 21: 357 -73.

Bellack A. S. (2006). Scientific and consumer models of recovery in schizophrenia: concordance, contrast, and implications. *Schizophr Bull* 32, 432-422.

Bica L., Crouch P. J., Cappai R.., and. White A. R., (2009) "Metallocomplex activation of neuroprotective signalling pathways as a therapeutic treatment for Alzheimer's disease," *Molecular BioSystems*, vol. 5, no. 2, pp. 134–142.

Brown S., Inskip H., Barraclough B. (2000). Causes of the excess mortality of schizophrenia. *Br J Psychiatry*. 177:212-7.

Cameron E, Pauling L. (1976). Supplemental ascorbate in the supportive treatment of cancer: prolongation of survival times in terminal human cancer. *Proc Natl Acad Sci*. 73:3685–9.

Carter A.S., Briggs-Gowan M.J., Davis N.O (2004). "Assessment of young children's social-emotional development and psychopathology: recent

advances and recommendations for practice". *J Child Psychol Psychiatry* 45 (1): 109–34.

Christen Y. (2000). "Oxidative stress and Alzheimer disease," *American Journal of Clinical Nutrition*, vol. 71, no. 2, pp. 621S–629S.

Cipriani A, Rendell JM, Geddes J (2009). "Olanzapine in long-term treatment for bipolar disorder". In Cipriani, Andrea. *Cochrane Database of Systematic Reviews (Online)* (1):CD004367. doi:10.1002/14651858.CD004367.pub2. PMID 19160237Davis J., Chen N., and Glick I. D.. A meta-analysis of the efficacy of second generation antipsychotics. *Arch Gen Psychiatry* 60, 553-564.

Clark LA, (2007). Assessment and diagnosis of personality disorder: perennial issues and an emerging reconceptualization" *Annu Rev Psychol* 58: 227-57

Coyle, J. T.; Puttfarcken, P. (2003) Oxidative stress, glutamate and neurodegenerative.

Cowen Mark (2011) Certain toxic trace elements may be elevated in bipolar disorder *J Trace Elem Med Biol,* Advance online publication

Department of Laboratory Medicine, University of Washington, Seattle (2004), *Am J Clin Pathol*; 121(Suppl 1):S64-S70.

Desai V and Kaler S.G. (2008) Role of copper in human neurological disorders, *J clinc Nutri* vol. 88 no. 3 855S-858S

Dexter, D. T.; Carter, C. J.; Agid, F.; Agid, Y.; Lees, A. J.;Jenner, P.; Marsden, C. D. (1986) Lipid peroxidation as a cause of nigral cell death in Parkinson's disease. *Lancet* 2:639–640.

Dexter, D. T.; Carter, C. J.; Wells, F. R.; Javoy-Agid, F.; Agid, Y.; Lees, A.; Jenner, P.; Marsden, C. D. (1989). Basal lipid peroxidation in substantia nigra is increased in Parkinson's disease. *J. Neurochem.* 52:381–389.

Elkashef, E.M., Doudet, D., Bryant, T., Cohen, R.M., Li, S. and Wyatt, R.J. (2000). 6-(18)F-DOPA PET study in patients with schizophrenia. *Psychiatry Research*, 100:1–11.

Food and Nutrition Board IOM, (2000) Dietary reference intakes for vitamin C, vitamin E, Selenium, and carotenoids. Washinton, DC: National Academy Press.

Fraga C, G. (2005) Relevance, essentiality and toxicity of trace elements in human health

Gamma A, Angst J, Ajdacic V, Eich D, Rossler W (2007). "The spectra of neurasthenia and depression: course, stability and transitions". *Eur Arch Psychiatry Clin Neurosci* 257 (2): 120-7.

Gazzaniga, MS., & Heatherton, T.F (2006). *Psychological Science* New York: W.W. Norton & Company

Grant BF, Hasin DS, Stinson FS, *et al.* (July 2004). "Prevalence correlates and disability of personality disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions". *J Clin Psychiatry* 65 (7): 948–58.

Gurney, M. E.; Pu, H.; Chiu, A. Y.; Dal Canto, M. C.; Polchow, C. Y.; Alexander, D. D.; Caliendo, J.; Hentati, A.; Kwon, Y. W.; Deng, H.; Chen, W.; Zhai, P.; Sufit, R. L.; Siddique, T. (1994); Motor neuron degeneration in mice that express a human Cu, Zn, superoxide dismutase mutation. *Science* 264:1772–1775.

Groleger U (2007). Off- label use of antipsychotics: rethinking "off-label". Psychiatr Danub 19, 350-353.

Geddes J., Freemantle N., Harrison P., and Bebbington P. (2000). Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta regression analysis. *BMJ* 321, 1371-1376.

Ghaemi S.N., Hsu D.J., Rosenquist K.J., Pardo T.B and Goodwin F.K (2006). Extrapyramidal side effect with atypical neuroleptics in bipolar disorder. *Prog Neuropsychopharma Biol Psychiatry* 30, 209-213.

Halliwell B., Gutteridge J.M. (1990) Role of free radicals and catalytic metal ions in human disease: An overview. Meth Enzymol; 186:1–85

Halliwell B. (1995) Oxidation of low-density lipoproteins: questions of initiation, propagation, and the effect of antioxidants. J Clin Nutr. 61:670–7S

Halliwell B, Cross C.E., Gutteridge JMC. (1996); Antioxidants in human health and disease. *Annu Rev Nutr*. 16:33–50.

Halliwell B., (1999) Antioxidant defence mechanisms: from the beginning to the end (of the beginning), Free Radic. Res. 31 261–272.

Halliwell B., (1999); Oxygen and nitrogen are pro-carcinogens, Damage to DNA by reactive oxygen, chlorine and nitrogen species: measurement, mechanism and the effects of nutrition, Mutat Res 443 37–52.

Halliwell B., (2001) Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment, *Drugs Aging* 18 685–716

Halliwell B. (2006). Oxidative stress and neurodegeneration: where are we now? *Journal of Neurochemistry* 97, 1634–1658.

Halliwell B, Gutteridge JMC: (2007) Free Radicals in Biology and Medicine 4th edition. *Oxford: Oxford University Press.*

Hegde M. L., M.Hegde P., M.F.Holthauzen L., Hazra T. K., Rao K.S.J., and Mitra S., (2010) "Specific inhibition of NEIL-initiated repair of oxidized base damage in human genome by copper and iron: potential etiological linkage to neurodegenerative diseases," *Journal of Biological Chemistry*, vol. 285, no. 37, pp.28812–28825.

Hole P.S., Darley R.L., Tonks A. (2011); Do reactive oxygen species play a role in myeloid E. Mariani, M.C. Polidori, A. Cherubini, P. Mecocci, (2005); Oxidative stress in brain aging, neurodegenerative and vascular diseases: an overview, J. Chromatogr. B Analyt. Technol Biomed. Life Sci. 827 65–75.

Hadjigeorgiou G. (2008). Oxidative stress, mitochondrial dysfunction and Alzheimer's disease. *Annals of General Psychiatry*, 7(Suppl 1):S75

Horacek G., OLeary D.H., Zaccro D., Haffner S., Kopecek M., Palenicek T., Dockery C., Mohr P. and Hoschl C (2006) Mechanism of action of

atypicalantipsychotic drugs and neurobiology of schizophrenia. *CNS Drugs* 20, 389-409.

Hasnain M., Vieweg W.V and Fredrickson S.K (2010) Metformin for atypical antipsychotic-induced weight gain and glucose metabolism deregulation: review of the literature and clinical suggestions, *CNS Drug* 24, 193-206.

Ince, P. G.; Shaw, P. J.; Candy, J. M.; Mantle, D.; Tandon, L.; Ehmann, W. D.; Markesbery, W. R. (1994); Iron, selenium, glutathione peroxidase activity are elevated in sporadic motor neuron disease. *Neurosci. Lett.* 182**:**87–90.

International Diabetes Federation (IDF). *The IDF Consensus Worldwide Definition ofMetabolicSyndrome*.DF, (2006)http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf.

Insel T.R and Wang P.S (2010) Rethinking mental illness. *JAMA* 303, 1970-1971Mertz, W. (1981). The essential trace elements. Science . 213: 1332-1338.

Keen C.L., Uriu-Hare JY, Hawk SN, Jankowski MA, Daston G.P. (1998). Effect of copper deficiency on prenatal development and pregnancy outcome. *Am. J. Clin. Nutr.* 67:1003S–11.

Kell D. B. (2010) "Towards a unifying, systems biology understanding of large-scale cellular death and destruction caused by poorly liganded iron: Parkinson's, Huntington's, Alzheimer's, prions, bactericides, chemical toxicology and others as examples," *Archives of Toxicology*, vol. 84, no. 11, pp. 825–889.

Koller E.A and Doraiswamy P.M (2002) Olanzipine-associated diabetes mellitus. *Pharmacotherapy* 22,841-852.

Koller E. A., Cross J.T., Doraiswamy P. M and Malozowski S N (2003). Pancreatitis associated with atypical antipsychotics from the food and Drug Administratio's MedWatch Surveillancesystem and published reports. Pharmacotherapy 23, 1123-1130

Konopaske G. T., Dorph-Petersen K. A., Sweet R. A., Pierri J N., Zhang W., Sampson A.R. and Lewis D.A (2008) Effect of chronic antipsychotic exposure and astrocyte and oligodendrocyte numbers in macaque monkeys. *Biol Psychiatry* 63, 759-765

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005). "Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication". *Arch. Gen. Psychiatry* 62 (6): 593–602.

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE (2005)."Prevalence, Severity, and Comorbidity of Twelve-month DSM-IV Disorders in the National Comorbidity Survey Replication (NCS-R)". *Arch. Gen. Psychiatry* 62 (6): 617–27.

Koran LM, Sheline Y, Imai K, Kelsey TG, Freedland KE, Mathews J,(2002),. Medical disorders among patients admitted to a public-sector psychiatric inpatient unit. *Psychiatr Serv*.; 53:1623-5.

Kumar N, Gross J.B.J., Ahlskog J.E. (2004). Copper deficiency myelopathy produces a clinical picture like subacute combined degeneration. *Neurology* 63:33–39.

Leucht S., Wahlbeck K., Hamann J., and Kissling W. (2003) New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet* 361, 1581-1589.

Mac Suibhene, S (2009); What makes "a new mental illness". The cases of solastalgia and hubris syndrome". *Cosmos and History* 5 (2): 210-225

Maritim A.C, Sanders R.A, Watkins JB. (2003). Diabetes, oxidative stress, and antioxidants: a review. *J Biochem Molec Toxicol*; 17:24–38.

Markesbery, W. R.; Ehmann, W. D.; Candy, J. M.; Ince, P. G.; Shaw, P. J.; Tandon, L.; Deibel, M. A. (1995); Neutron activation analysis of trace elements in motor neuron disease spinal cord. *Neurodegeneration* 4:383–390.

Martin, S.J.,Grimwood, P.D. and Morris, R.G.M. (2000). Synaptic plasticity and memory: An evaluation of the hypothesis. *Annual Review of Neuroscience*, 23:649–711.

Mats J, Pérez G, Cristina D, Castro J. (1999) Antioxidant enzymes and human diseases. Clin Biochem.; 32:595–603

Mills, X. P. Dong, F. Wang, and H. Xu, (2010) "Mechanisms of brain iron transport: insight into neurodegeneration and CNS disorders," *Future Medicinal Chemistry*, vol. 2, no. 1, pp. 51–64.

Morey LC, Hopwood CJ, Gunderson JG. (July 2007). "Comparison of alternative models for personality disorders". *Psychol Med* 37 (7): 983–94.

"Mental Health: Types of Mental Illness". WebMD. Retrieved 2011-09-09.

Murphy B.P., Chung Y.C., Park T.W. and McGorry P.D. (2006) Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review, *Schizophr* Res 88, 5-25.

Mariani, E., Polidori, M.C., Cherubini, A., Mecocci, P., (2005). Oxidative stress in brain.

Nanami, M.; Ookawara, T; Otaki, Y; Ito, K; Moriguchi, R; Miyagawa, K; Hasuike, Y; Izumi, M. (2005). "Tumor necrosis factor-α-induced iron sequestration and oxidative stress in human endothelial cells". *Arteriosclerosis, thrombosis, and vascular biology*25 (12): 2495–2501

National Institute for Health and Clinical Excellence (2009). *Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care (CG82)*. NICE.

Niedowicz D, Daleke D. (2005); The role of oxidative stress in diabetic complications. Cell Biochem Biophys.; 43:289–330

Nordberg J, Arnér ESJ. (200); Reactive oxygen species, antioxidants, and the mammalian thioredoxin system. Free Radic Biol & Medic. 31:1287–312.

Nyike CU, Crum RM, Lee HB, Lyketsos CG (2003), *Eaton WW.* Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol*.; 158:1139-47.

Ng F., Berk M., Dean O., Bush AI. (2008). Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. *Int J Neuropsychopharmacol.* 2008 Sep;11(6):851-76.

Olanow, C. W. A radical hypothesis for neurodegeneration. *Trends Neurosci.* 16:439–444; 1993.

Olga P. García, D. Ronquillo M. Del C C, Mariela C, Kurt Z L and Jorge L R.(2012). Zinc, Vitamin A, and Vitamin C status are associated with leptin concentrations and obesity in mexican women: results from a cross-sectional study Oxidative stress. From: http://www.plantstress.com/Articles. Accessed: Dec 2010.

Osei, Y. (1994). Psychiatric Service in a Developing Country - The Case of Ghana Curare, 17, 39-43.

Owiredu W.K., Appiah-Poku J., Adusei-Poku F., Amidu N., and Osei Y (2009). The impact of glucose and cholesterol levels on the manifestation of Psychiatric disorders. *Pak J Biol Sci* 12, 252-257.

Owiredu W.K.B.A., Osei O., Amidu N., Appiah-Poku J. and OseiY (2012). Prevalence of metabolic syndrome among Psychiatric Patients in the Kumasi Metropolis, Ghana. *Journal of Medical and Biomedical Sciences* 1(2): 38-49.

Pena MM, Lee J, Thiele DJ. (1999). A delicate balance: homeostatic control of copper uptake and distribution. *J. Nutr.* 129:1251–60

Pickering RP, Grant BF, Chou SP, Compton *WM* (2007). Are overweight, obesity, and extreme obesity associated with psychopathology? Results from the national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry.*; 68:998-1009.

Phillips M, Cataneo RN, Cheema T, Greenberg J. (2004) Increased breathe biomarkers of oxidative stress in diabetes mellitus. *Clin Chim Acta.*; 344:189–94.

Ponka P. (1999). Cellular iron metabolism. *Kidney Int.* 69(Suppl.):S2–11

Prodan CI, Bottomley SS, Holland NR, Lind SE. (2006). Relapsing hypocupraemic myelopathy requiring high-dose oral copper replacement. *J. Neurol. Neuros. Psychiatry.* 77:1092–93.

Prohaska J.R, Brokate B. (2002). The timing of perinatal copper deficiency in mice influences offspring survival. *J. Nutr.* 132:3142–45.

Pedneault K.S. (2009).Psychiatric Disorder - A Definition of Psychiatric Disorder *Health's Disease and Condition 3*(1): 21-22

Read u. M. And doku v. C.k (2012), Mental health research in Ghana: A Literature review retrieved from www.ghanamedj.org/suparticles/june2012/mental%20health.pdf.

Ried Douglas L., McConkey Joel R; Bengtson Michael A., Garman Patrick M. Hsu Chienning, Rahnavard Farzad (2007). Weight and blood pressure changes after switching SGAs in a population of veterans with schizophrenia-related disorders *J Am Pharm Assoc.* ;47:156-164.

Ralph, A., and McArdle, H.J. (2001). Copper metabolism and requirements in the pregnant mother, her fetus, and children. New York: International Copper Association

Rowe L. (2009). DNA damage-induced reactive oxygen species: A genotoxic stress response. PhD Thesis, Emory University, Georgia, USA.

Saha S., Chant D., Welham J., McGrath J (May 2005). "A Systematic Review of the Prevalence of Schizophrenia"

Sandstead, H.H., Frederickson, C.J. and Penland, J.G. (2000). History of zinc as related to brain function. *Journal of Nutrition*, 130(2S Suppl):496S–502S.

Sayre L. M., Zelasko D. A., Harris P. L. R., Perry G., Salomon R.G., and Smith M. A., (1997) "4-Hydroxynonenal-derived advanced lipid peroxidation end products are increased in Alzheimer's disease," *Journal of Neurochemistry*, vol. 68, no.5, pp. 2092–2097,

Seifried HE, Anderson DE, Fisher EI, Milner JA. (2007) A review of the interaction among dietary antioxidants and reactive oxygen species. *J Nutr Biochem.* ; 18:567–79.

Sies H. (1997); Oxidative stress: oxidants and antioxidants. *Exp Phys*. 82:291–5.

Smith M. A., Harris P. L. R., Sayre L. M., and Perry G., (1997) "Iron accumulation in Alzheimer disease is a source of redoxgenerated free radicals," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 18, pp. 9866–9868,

Somers JM, Goldner EM, Waraich P, Hsu L (February 2006). "Prevalence and incidence studies of anxiety disorders: a systematic review of the literature". *Can J Psychiatry*:Pp 100-13.

Shokrzadeh M., Ghaemian A., Salehifar E. (2009),. Serum zinc and copper levels in ischemic cardiomyopathy. *Biol Trace Elm Res*.; 127(2): 116-123.

Standard Treatment Guidelines. Ministry of Health Ghana National Drugs Programme
(GNDP). 2004.

Thakore JH, Mann JN, Vlahos I, Martin A, Reznek R (2002). Increased visceral fat distribution in drug-naive and drug-free patients with schizophrenia.*Int J Obesity* ; 26: 137-41

The United States Department of Health and Human Services. Mental Health: A Report of the Surgeon General. "Chapter 2: The Fundamentals of Mental Health and Mental Illness." pp 39 Retrieved May 21, 2012

Trimble, M. (2001); "Uncommon psychiatric syndromes, 4th edn: Edited by M David Enoch and Hadrian N Ball (Pp 260, pound 25. 00). Published by Arnold Publishers, London, ISBN 0-340-76388-4". Journal of Neurology, Neurosurgery & Psychiatry 73 (2): 211-212.

TIETZ, Fundamentals of clinical Chemistry, sixth Edition (2008), page; 476

Torgersen S., Kringlen E and Cramer V (2001). The prevalence of personality disorders in a community sample. *Arch Gen Psych* 58, 590-596

Torrey E.F and Swalwell C.I (2009) Fatal olanzipine-induced ketoacidosis. *Am J Psychiatry*160, 2241.

Tsaluchidu S. et al. (2008). Fatty acids and oxidative stress in psychiatric disorders. *BMC Psychiatry*. 8(Supplement 1), s5

Tudor, R., Zalewski, P.D., Ratnaike, R.N. (2005) Zinc in health and chronic disease.*J Nutr Health Aging.* 9(1):45-51.

Twumasi, P.A. (1988). Social Foundations of the Interplay Between Traditional and Modern Medical Systems. An Inaugural Lecture at the University of Ghana, Legon.

Tuunainen A., Whalbeck K. and Gilbody S.M (2000). Newer atypical antipsychotic medication versus clozapine for schizophrenia. *Cochrane Database Syst Rev,* CD000966.

US National Institute of Mental Health (2006) The Numbers Count: Mental Disorders in America Retrieved May 2011.

Vallee, B., Coleman, J., Auld, D. (1991) Zinc fingers, zinc clusters, and zinc twists in DNA binding protein domains. *Proc Natl Acad Sci*. USA 88: 999-1003

Vallee, B., Falchuk, K. (1993) The biochemical basis of zinc physiology. *Physiol Rev*. 73: 79-118

Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J (2007). Free radicals and antioxidants in normal physiological functions and human disease. *International Journal of Biochemistry and Cell Biology* 39, 44–84.

Waraich P, Goldner EM, Somers JM, Hsu L (2004). "Prevalence and incidence studies of mood disorders: a systematic review of the literature". *Can J Psychiatry* Pp 124–38.

Waris G, Alam K. (1998); Attenuated antigenicity of ribonucleoproteins modified by reactive oxygen species. Biochem Molec Biol Int. 45:33–45.

Weiser, M., Levkowitch, Y., Neuman, M. and Yehuda, S. (1994). Decrease of serum iron in acutely psychotic schizophrenic patients. *International Journal of Neuroscience*, 78(1):49–52.

World Health Organization (1999) Definition, diag-nosis and classification of diabetes mellitus and its complications: report of a WHO Consultation. Part 1: diagnosis and classifi-cation of diabetes mellitus. Geneva, Switzerland: World Health Organization.

WHO International Consortium in Psychiatric Epidemiology (2000) Cross-national comparisons of the prevalences and correlates of mental disorders, *Bulletin of the World Health Organization* v.78 n.4

World_Health_Organization (2003). Traditional Medicine- Growing Needs and Potential. Geneva, World Health Organization

Wiedau-Pazos, M.; Goto, J. J.; Rabizadeh, S.; Gralla, E. B.; Roe, J. A.; Lee, M. K.; Valentine, J. S.; Bredesen, D. E. (1996); Altered reactivity of superoxide dismutase in familial amyotrophic lateral sclerosis. *Science* 271:515–518.

Willett WC, MacMahon B. (1984) Diet and cancer - an overview. N Engl J Med. ; 310:633–8.

Willson L (2011) cadmium the pseudo-masculine mineral and the early death mineral, centre for development article.

Wittchen HU, Jacobi F (August 2005). "Size and burden of mental disorders in Europe—a critical review and appraisal of 27 studies". *Eur Neuropsychopharmacol* 15 (4): 357–76.

Wong, P.; Pardo, C. A.; Borchelt, D. R.; Lee, M. K.; Copeland, N. G.; Jenkins, N. A.; Sisodia, S. S.; Cleveland, D. W.; Price, D. L. (1995); An adverse property of a familial ALS-linked SOD-1 mutation causes motor neuron disease characterized by vacuolar degeneration of mitochondria. *Neuron* 14:1105–1116.

World Cancer Research Fund / American Institute for Cancer Research. (1997) Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR.

World Health Organization Gender disparities and mental health: The Facts Last retrieved January 12, 2012.

Xiongwei Zhu Adam D. Cash, Ravi Srinivas, Catherine A. Rottkamp, , Marta A. Taddeo, Gjumrakch Aliev, Hisashi Fujioka, Craig S. Atwood, Lawrence M. Sayre, Rudolph J. Castellani, Mark A. Smith, George Perry, and Akihiko Nunomura (2004) Metal Homeostasis and Its Relation to Oxidative Stress in Alzheimer's Disease Redox-Genome Interactions in Health and Disease.

Zhang XY, Zhou DF, Cao LY, (2003), "The effects of risperidone treatment on superoxide dismutase in schizophrenia". *J Clin Psychopharmacol*; 23:128–131

STUDY OF TRACE ELEMENTS LEVELS AND OXIDATIVE STRESS IN GHANAIAN PSYCHIATRIC PATIENTS RECEIVING MEDICATION AND TREATMENT NAIVE PATIENTS

A THESIS SUBMITTED IN FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

In the

Department of Molecular Medicine,
School of Medical Sciences

by

EDWARD EYIPE ESSUMAN BSc. (HONS.)

KWAME NKRUMAH UNIVERSITY OF SCIENCE & TECHNOLOGY,

KUMASI

AUGUST, 2012