METABOLIC SYNDROME AND OXIDATIVE STRESS IN GHANAIAN PSYCHIATRIC PATIENTS: CONVENTIONAL VS. ATYPICAL ANTIPSYCHOTIC MEDICATIONS

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

MASTER OF PHILOSOPHY

In the

Department of Molecular Medicine,
School of Medical Sciences

by

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AUGUST, 2010

DECLARATION

The experimental work described in this thesis was carried out at the Department of Molecular Medicine, KNUST. This work has not been submitted for any other degree.

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ABSTRACT

Metabolic syndrome (MetS), a major public health problem linked to cardiovascular and other morbidities, has gained a significant importance in clinical settings and patients with severe mental illnesses who are at higher risk for different components of this syndrome due to their illness and its treatment require careful and regular monitoring in this regard. Even though MetS has been found to be more prevalent among psychiatric patients than among any other population group, no data exist on its prevalence in Ghanaian psychiatric patients. This study seeks to find the prevalence of the MetS, its individual components and oxidative stress in psychiatric patients on antipsychotics (conventional and atypical) compared to newly diagnosed psychiatric patients. This cross-sectional study of patients attending psychiatric department of the Komfo Anokye Teaching Hospital (KATH) between February 2009 and July 2010. A total of 200 psychiatric patients comprising 100 newly diagnosed antipsychotic naïve patients and 100 patients on antipsychotic medication were sampled for the study. Prevalence of MetS diagnosed using the World Health Organization (WHO), International Diabetes Federation (IDF) and the National Cholesterol Education Programme, Adult Treatment Panel III (NCEP ATP III) criteria for defining MetS was employed. The overall prevalence of MetS was 11.5%, 13.5% and 15.5% using NCEP ATP III, WHO and IDF criteria respectively. The prevalence was significantly higher among psychiatric patients on treatment as compared to treatment naïve group using NCEP ATP III (21.0% vs. 2.0%; $p < 0.0001$) and IDF (29.0% vs. 2.0%; $p < 0.0001$) criteria but not WHO (13.0% vs. 14.0%; $p = 0.8372$). Irrespective of the criteria used, the prevalence of MetS was higher among patients on atypical vs. typical antipsychotic medication (i.e. 44.4% vs. 18.7% for NCEP ATP III; 22.2% vs. 12.1% for WHO and 56.6% vs. 27.5% for IDF), however, these differences did not reach a significant level. Oxidative stress appears to confer some sort of protection against the development of MetS as defined by the IDF criteria among these subjects. Prevalence of MetS in this population was double that in the general Ghanaian population. Prevalence of MetS was not only highly prevalent among Ghanaian patients treated with antipsychotic drugs, it was also higher among patients on atypical vs. conventional antipsychotic medication. Regular monitoring of metabolic parameters should be considered as a standard part of their medical care.

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 very grateful to Dr. Yaw Osei of the Psychiatric Unit, Komfo Anokye Teaching Hospital who welcomed me to his department and co-supervised me to the best of his abilities. I would want to say thank you for your words of encouragement, tolerance, and guidance and especially, the excellent supervisory role you performed to help me with my studies throughout my stay at the department. Working with you has been an excellent learning experience.

My sincere gratitude also goes to Prof. Rev. Fr. John Appiah- Poku of the School of Medical Sciences, KNUST for the useful suggestions that always served as an eye opener for me.

I am indebted to Dr. Nafiu A. Amidu for the precious time, all the support, advice and encouragement he gave during my study.

Finally, my heartfelt gratitude goes to my family and my very good friend Lawrence Quaye as well as all the wonderful friends who gave me the support throughout my study who were not mentioned for want of space.

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INTRODUCTION

1.1 GENERAL INTRODUCTION

Metabolic syndrome is a multi-system disorder characterized by clustering of abnormalities which increase the risk of cardiovascular disorders (CVD). The abnormalities include those of glucose homeostasis and metabolism, obesity, hyperlipidaemia and hypertension (Holt *et al.*, 2004; Lieberman, 2004; Toalson *et al.*, 2004; Meyer *et al.*, 2005; Blaha and Elasy, 2006). Risk factors for cardiovascular disorders and rates of physical disorders in the psychiatric population are increased partly due to low levels of help-seeking (Phelan *et al.*, 2001) and lifestyle factors such as poor diet, reduced physical activity and smoking. Mortality rates of about 2 to 3 times have also been reported in psychiatric patients compared to the general population (Lesage *et al.*, 1990; Brown *et al.*, 2000). In a study on the risk of coronary heart disease (CHD) and stroke in addition to lifestyle factors in psychiatric patients, McCreadie, (2003) reported an increased (9.6%) mean 10-year risk of coronary heart disease compared to the general population (6.4%) as was the risk of stroke (4.1%).

In such a population with higher physical morbidity compared to the general population, there is gradually an increasing concern about the contribution of antipsychotic medication to the prevalence of metabolic syndrome and its components especially since the introduction of the atypical (second generation) antipsychotic medications. Recent studies have indicated an increase in the prevalence of weight gain, glucose intolerance and hyperlipidaemia and in a few cases, hypertension following antipsychotic use in psychiatric patients. Heiskanen et al., (2003) reported the diagnosis of metabolic syndrome in 13 (37%) out of 35

patients with schizophrenia treated with antipsychotic medication and Mackin et al., (2007) reported increased prevalence of metabolic syndrome and cardiovascular risk in 90 people treated with antipsychotics, compared to 92 age and gender matched controls. Correl et al., (2006) also reported that metabolic syndrome was present in 137 (37.3%) out of 367 adults treated with second generation antipsychotics and was significantly associated with the 10-year risk of Coronary Heart disease (CHD) events.

Atypical antipsychotics have become the basis of treatment of psychiatric disorder. However their efficacy in comparison to conventional antipsychotics is being hotly debated and has been the subject of much research activity. The meta-analysis by Davis et al. (2003) suggested that some of the atypical antipsychotics (clozapine, amisulpride, risperidone and olanzapine) were more efficacious than conventional neuroleptics, but more recent studies indicate otherwise. Lieberman et al. (2005) indicated that olanzapine was most effective when rates of discontinuation were considered (but was also associated with the most weight gain and dyslipidemia) and the conventional antipsychotic perphenazine was of similar efficacy to quetiapine, risperidone and ziprasidone in a Clinical Antipsychotic Trial of Intervention Effectiveness. According to McEvoy et al. (2006), clozapine was found to be more effective than the other atypical antipsychotics in the Phase 2 of the same study. Jones et al. (2006) established that atypical antipsychotic drugs did not offer any significant advantage over the use of conventional antipsychotics in terms of cost.

Alongside the efficacy debate, there has recently been considerable interest and concern about the metabolic abnormalities associated with atypical antipsychotic use (American Diabetes Association, 2004). The issues being discussed are whether

these metabolic abnormalities are seen only with antipsychotic treatment, if there is a difference between atypical and conventional antipsychotics in terms of these side effects and about the differing metabolic profiles of the various atypical antipsychotics.

1.2 JUSTIFICATION

Psychiatric disorders are on the increase in Ghana (Turkson, 1998) due probably to the abuse of psychoactive substances such as cannabis, heroin etc. In a previous study by Owiredu et al. (2009), diabetes and dyslipidaemia have been linked with psychiatric disorders. In a study that examined the dyslipideamia following treatment with antipsychotic medication, hypertriglycerideamia and reduced HDL cholesterol were not only associated with the newly diagnosed psychiatric patients, the effects of which become more pronounced among those on antipsychotic medication (Owiredu *et al.*, 2009). Abnormalities in other factors, including blood pressure, body mass index and waist-to-hip ratio have also been associated with mental illness. There is however paucity of data on these in Ghana.

Many of the research works done elsewhere have linked the metabolic abnormalities on psychiatric patients to the psychotherapeutic drugs administered. Despite the fact that the side effects of most of these antipsychotic drugs had been established, they are also affected by age, sex, cultural practices, diet, environment, ethnicity and the genetic make-up of the individual. These factors are also emerging as an important risk factor in the development of metabolic syndrome and a recent study in UK found that South Asians, living in the UK have a higher prevalence of diabetes, coronary heart disease and cardiovascular deaths with a three to four fold increase as compared to the local white population (Mukhopadhyay et al., 2005).

While recent reports are showing an increase of metabolic syndrome among the general population, a growing concern is being expressed about this problem among the mentally-ill (Citrome et al., 2005). It is an agreed fact that chronic mentally-ill patients are more vulnerable to physical health problems and show significant increase in relation to their physical health as compared to the general population (Phelan *et al.*, 2001; Ohlsen *et al.*, 2005). A look at the risk factors contributing to the high prevalence of medical health problems in the mentally-ill, the presence of metabolic syndrome emerges as an important risk factor for Cardiovascular and Diabetic morbidity. It is generally estimated that metabolic syndrome is especially common in patients with severe mental illnesses.

1.3 AIMS OF THE STUDY

Due to the paucity of studies of metabolic syndrome as a whole in psychiatric patients in Ghana, this study seeks to find the prevalence of the metabolic syndrome, its individual components and oxidative stress in psychiatric patients on antipsychotics (conventional and atypical) compared to newly diagnosed psychiatric patients using the World Health Organization, International Diabetes Federation and the National Cholesterol Education Programme, Adult Treatment Panel III criteria for defining metabolic syndrome.

1.4 SPECIFIC OBJECTIVES

1. To compare the prevalence of metabolic syndrome and its components among newly diagnosed psychiatric patients and those on treatment

2. To compare the prevalence of metabolic syndrome and its components among psychiatric patients on conventional and atypical antipsychotic medication.

3. To determine the possible risk factors for the development of metabolic syndrome among this study population.

Chapter 2

LITERATURE REVIEW

2.1 DEFINITION OF MENTAL ILLNESS/MENTAL DISORDER

A mental disorder or mental illness is a psychological or behavioural pattern associated with distress or disability that occurs in an individual and is not a part of normal development or culture.

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 standards are widely accepted.

2.1.1 Epidemiology

Mental disorders are common. World wide more than one in three people in most countries report sufficient criteria for classification as mentally ill at some point in their life (WHO, 2000). In the United States 46% of the population qualifiy for a mental illness at some point (Kessler *et al.*, 2005). A survey has indicated that anxiety disorders are the most common, followed by mood disorders while substance disorders and impulse-control disorders are consistently less prevalent (World Mental Health Survey Initiative). The rates however varied by region (Demyttenaere *et al.*, 2004). Such statistics are widely believed to be underestimates, due to poor diagnosis (especially in countries without affordable

access to mental health services) and low reporting rates, in part because of the predominant use of self-report data rather than semi-structured instruments. Actual lifetime prevalence rates for mental disorders are estimated to be between 65% and 85%. 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 *et al.*, 2004). In the United States the frequency of mental disorder is: anxiety disorder (28.8%), mood disorder (20.8%), impulse-control disorder (24.8%) or substance use disorder (14.6%) (Kessler *et al.*, 2005). A 2004 cross-Europe study found that approximately one in four people reported meeting the 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 the criteria within a 12-month period. Women and younger people of either gender showed more cases of the disorder (Alonso *et al.*, 2004). A 2005 review of surveys in 16 European countries found that 27% of adult Europeans are affected by at least one mental disorder in a 12 month period (Wittchen and Jacobi, 2005).

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 (Saha *et al.*, 2005). Studies of the prevalence of personality disorders (PDs) have been fewer and on a 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 (Torgersen *et al.*, 2001). A US survey that

incidentally screened for personality disorder found a rate of 14.79% (Grant *et al.*, 2004).

2.2 BRIEF HISTORY OF PSYCHIATRIC SERVICES 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 (Foster, 1962). 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. 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).

2.2.1 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 general hospitals and some private psychiatric hospitals while the community component is practiced at the primary care level, championed by Community Psychiatric Nurses (CPNS)

2.2.2 Psychiatric Hospitals

There are currently three psychiatric hospitals in the country namely:

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.

2.2.3 Private Services

There are two private hospitals in Kumasi Ashanti Region – **Pankrono Neuro-Psychiatric hospital** and **Adom Clini**c at Santasi. In Accra, there is one private

hospital –**Valley View Clinic** and in the Port city of Tema, **The Alberto clinic**. All the private clinics are manned by psychiatric specialists except Adom Clinic which is manned by an experienced nurse.

In the Komfo Anokye Teaching Hospital in Kumasi, which is a public institution, there is the Psychiatric Unit that attends to psychiatric patients which is manned by psychiatric specialists as well as experienced psychiatric nurses.

2.2.4 Epidemiology

Given the absence of hard community based data for mental illness in Ghana, extrapolations are made from WHO estimates. Thus:

- 25% of the population suffers from neuro-psychiatric conditions during their lifetime.
- 10% of any population is suffering from neuro-psychiatric conditions at any time.
- 1% of that population is suffering from severe mental illness

Given the total population of about 20 million people in Ghana the following should be true:

- 5,000,000 will suffer from neuro-psychiatric conditions during their lifetime.
- 2,000,000 will suffer from neuro-psychiatric conditions at a given time.
- 200,000 will suffer from severe mental illness.

2.3 CLASSIFICATION OF MENTAL DISORDERS

The definition and classification of mental 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-IV) produced by the American Psychiatric Association (APA). Both list categories of disorder and provide standardized criteria for diagnosis (Akiskal and Benazzi, 2006). 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.*

2.3.1 Disorders

There are many different categories of mental disorder and many different facets of human behaviour and personality that can become disordered.

Anxiety or fear that interferes with normal functioning may be classified as an anxiety disorder (Akiskal and Benazzi, 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 disorders involving unusually intense and sustained sadness, melancholia or despair is known as Major depression 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.

Whether unipolar and bipolar mood phenomena represent distinct categories of disorder, or whether they usually mix and merge together along a dimension or spectrum of mood, is under debate in the scientific literature (Akiskal and Benazzi, 2006).

Patterns of belief, language use and perception 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 cut-off criteria.
Personality—the fundamental characteristics of a person that influence his or her thoughts and behaviours across situations and time—may be considered disordered if judged to be abnormally rigid and maladaptive. Categorical schemes list a number of different such personality disorders, including those sometimes classed as eccentric (e.g. paranoid, schizoid and schizotypical personality disorders), to those sometimes classed as dramatic or emotional (antisocial, borderline, histrionic or narcissistic personality disorders) or those seen as fear-related (avoidant, dependent, or obsessive-compulsive personality disorders). 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 behaviours that resolve in short periods, and maladaptive temperamental traits that are more stable (Clark, 2007).

Sleep disorders such as insomnia involve disruption to normal sleep patterns, or a feeling of tiredness despite sleep appearing normal.

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, may be 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 behavioural addictions, such as gambling addiction, may be classed as a 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), when it persists despite significant problems related to the use, may be defined as a mental disorder termed substance dependence or substance abuse (a broader category than drug abuse). The DSM does not currently use the common term drug addiction and the ICD simply talks about "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.

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.

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.

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.

Disorders appearing to originate in the body, but thought to be mental, are known as somatoform disorders, including somatization disorder and conversion disorder. There are also disorders of the perception of the body, including 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).

2.4 CAUSES OF MENTAL ILLNESS

Mental disorders can arise from a combination of sources. In many cases there is no single accepted or consistent cause currently established. A common belief even to this day is that disorders result from genetic vulnerabilities exposed by environmental stressors. However, it is clear enough from a simple statistical

analysis across the whole spectrum of mental health disorders at least in western cultures that there is a strong relationship between the various forms of severe and complex mental disorder in adulthood and the abuse (physical, sexual or emotional) or neglect of children during the developmental years.

Studies have indicated that genes often play an important role in the development of mental disorders, although the reliable identification of connections between specific genes and specific categories of disorder has proven more difficult. Environmental events surrounding pregnancy and birth have also been implicated. Traumatic brain injury may increase the risk of developing certain mental disorders. There have been some tentative inconsistent links found to certain viral infections (Yolken and Torrey, 1995), to substance misuse, and to general physical health. Abnormal functioning of neurotransmitter systems has been implicated, including serotonin, norepinephrine, dopamine and glutamate systems. Differences have also been found in the size or activity of certain brain regions in some cases. Psychological mechanisms have also been implicated, such as cognitive (e.g. reason), emotional processes, personality, temperament and coping style. Social influences have been found to be important, including abuse, bullying and other negative or stressful life experiences. The specific risks and pathways to particular disorders are less clear, however. Aspects of the wider community have also been implicated, including employment problems, socioeconomic inequality, lack of social cohesion, problems linked to migration, and features of particular societies and cultures.

2.5 DIAGNOSIS

Many mental health professionals, particularly psychiatrists, seek to diagnose individuals by ascertaining their particular mental disorder. Some professionals and clinical psychologists may avoid diagnosis in favour of other assessment methods such as formulation of a client's difficulties and circumstances.

The majority of mental health problems are actually assessed and treated by family physicians during consultations, who may refer on for more specialist diagnosis in acute or chronic cases. Routine diagnostic practice in mental health services typically involves an interview (which may be referred to as a mental status examination), where judgments are made of the interviewee's appearance and behaviour, self-reported symptoms, mental health history, and current life circumstances. The views of relatives or other third parties may be taken into account. A physical examination to check for ill health or the effects of medications or other drugs may be conducted.

Psychological testing is sometimes used via paper-and-pen or computerized questionnaires, which may include algorithms based on ticking off standardized diagnostic criteria, and in rare specialist cases neuro-imaging tests may be requested, but these methods are more commonly found in research studies than routine clinical practice (Davies, 1997). Time and budgetary constraints often limit practicing psychiatrists from conducting more thorough diagnostic evaluations (Kashner *et al.*, 2003). It has been found that most clinicians evaluate patients using an unstructured, open-ended approach, with limited training in evidence-based assessment methods, and that inaccurate diagnosis may be common in routine practice (Shear *et al.*, 2000). Mental illnesses involving hallucinations or delusions (especially schizophrenia) are prone to misdiagnosis in developing countries due to the presence of psychotic symptoms instigated by nutritional deficiencies.

Comorbidity is very common in psychiatric diagnoses, i.e. the same person given a diagnosis in more than one category of disorder.

2.6 MANAGEMENT

Treatment and support for mental disorders is provided in psychiatric hospitals, clinics or any of a diverse range of community mental health services. In many countries services are increasingly based on a recovery model that is meant to support each individual's independence, choice and personal journey to regain a meaningful life, although individuals may be treated against their will in a minority of cases. There are a range of different types of treatment and what is most suitable depends on the disorder and on the individual. Many things have been found to help at least some people and a placebo effect may play a role in any intervention or medication.

2.6.1 Psychotherapy

A major option for many mental disorders is psychotherapy. There are several main types. Cognitive behavioural therapy (CBT) is widely used and is based on modifying the patterns of thought and behaviour associated with a particular disorder. Psychoanalysis, addressing underlying psychic conflicts and defenses, has been a dominant school of psychotherapy and is still in use. Systemic therapy or family therapy is sometimes used, addressing a network of significant disorders as well as an individual. Some psychotherapies are based on a humanistic approach. There are a number of specific therapies used for particular disorders, which may be offshoots or hybrids of the above types. Mental health professionals often employ an eclectic or integrative approach. Much may depend on the therapeutic relationship, and there may be problems with trust, confidentiality and engagement.

2.6.2 Medication

A major option for many mental disorders is psychiatric medication and there are several main groups. Antidepressants are used for the treatment of clinical depression as well as often for anxiety and other disorders. A common example of antidepressants is Amytriptyline. Anxiolytics are used for anxiety disorders and related problems such as insomnia. Mood stabilizers are used primarily in bipolar disorder. Antipsychotics are mainly used for psychotic disorders, notably for positive symptoms in schizophrenia. Despite the different conventional names of the drug groups, there may be considerable overlap in the disorders for which they are actually indicated, and there may also be off-label use of medications.

2.7 ANTIPSYCHOTICS AND TYPES

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. These include serotonin-dopamine antagonists, multi-acting receptor-targeted antipsychotics (MARTA, those targeting several systems), and dopamine partial agonists, which are often categorized as atypical (Horacek *et al.*, 2006).

2.8 USAGE

Common conditions with which antipsychotics might be used include 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. 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. 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.

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.

2.9 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 hyperprolactinaemia (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". 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), 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 that 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.

2.10 CONVENTIONAL VERSUS ATYPICAL ANTIPSYCHOTICS

While the atypical (second-generation) antipsychotics 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, and 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 CATIE 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.

2.10.1 Common Antipsychotics

2.10.1.1 First Generation Antipsychotics

Butyrophenones

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

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)

Thioxanthenes

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

2.10.1.2 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 maintenance of 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-HT2A 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)

2.11 DRUG ACTION

All antipsychotic drugs tend to block D2 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 mesocortical pathway, tuberoinfundibular pathway, and the nigrostriatal pathway. Blocking D2 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 5HT2A, C and 5HT1A 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 why some of them can benefit the "negative symptoms" of schizophrenia (Murphy *et al.*, 2006).

2.12 METABOLIC SYNDROME IN PATIENTS WITH SEVERE MENTAL ILLNESSES

The connection between severe mental illness and the metabolic syndrome is emerging as a public health issue of importance to both mental health and primary care practitioners. Originally identified by Reaven (1992) as syndrome X or the insulin resistance syndrome, the magnitude of public health impact of the

metabolic syndrome is reflected by a recently estimated prevalence of approximately 24% in adults in the United States (Ford *et al.*, 2002). The prevalence of two basic components of this syndrome, obesity and diabetes, has clearly increased over the past decade throughout the United States (Mokdad *et al.*, 2003). Evidence is starting to accumulate that metabolic disturbances are common in patients with severe psychiatric illnesses (Dixon and K., 2003).

2.12.1 Definition of Metabolic Syndrome

Metabolic syndrome is by definition a multisystem disorder. *Metabolic syndrome*, *syndrome X* and the *insulin resistance syndrome* are all terms coined to describe the recognized clustering of metabolic and cardiovascular abnormalities including obesity, hypertension, dyslipidemia, hyperuricemia, and abnormalities of glucose homeostasis (i.e., insulin resistance, glucose intolerance, or diabetes mellitus).

Along with competing names for this syndrome, different groups have suggested different diagnostic criteria (Alberti and Zimmet, 1998; NCEP, 2001). Central or upper body obesity is more closely associated with the syndrome than is lower body obesity and waist circumference provides a surrogate measure for the visceral fat deposits that underlie this relationship. Likewise, high triglycerides and low high-density lipoprotein (HDL) cholesterol are specific blood lipid changes associated with metabolic syndrome. Oxidative stress results due to disturbed equilibrium between pro oxidants and antioxidants and play a role in pathophysiology of Diabetes and Cardiovascular diseases (Diaz *et al.*, 1997; Halliwell, 1997). One of the most frequently used biomarkers providing an indication of lipid peroxidation level is the plasma concentration of malondialdehyde (MDA), one of several by-products of lipid peroxidation processes (Nielsen *et al.*, 1997).

2.12.2 Pathophysiology of Metabolic Syndrome

The biochemical perturbations observed in the metabolic syndrome include changes in glucose tolerance and lipoprotein levels as well as alterations in inflammatory mediators and pro-coagulant factors. Multiple organ systems are affected, including adipose, muscle, hepatic, nervous and adrenal tissues, but from a clinical standpoint, the most important site of impact is the vasculature. Cumulative effects of classical risk factors such as glucose intolerance, dyslipidemia, and hypertension very likely contribute to increased risk of cardiovascular disease seen in individuals with the metabolic syndrome (Alberti and Zimmet, 1998). Hyperinsulinaemia, a surrogate for insulin resistance and a marker for metabolic syndrome, is, in itself, associated with a 2- to 3-fold increase in cardiovascular disease independent of classical risk factors (Howard *et al.*, 1996; Reaven, 2002). Other components of this syndrome that may contribute to a pro-atherogenic state include increased levels of plasminogen-activator inhibitor I (PAI-I), angiotensin II, interleukin-6 (IL-6), tumor necrosis factor α (TNFα), and others (Das, 2002; Dandona *et al.*, 2003). Impaired insulin responsiveness (i.e., insulin resistance) is presumed to be central to the metabolic syndrome and may provide the underlying process from which other abnormalities evolve (Reaven, 1993; Ford *et al.*, 2002). With resistance to insulin, unchecked lipolysis leads to increased delivery of free fatty acids to the liver for triglyceride synthesis and packaging into very low-density lipoprotein (VLDL) particles. Higher VLDL levels contribute to lower HDL levels because of the reciprocal exchanges between these lipoproteins mediated by cholesterol ester transfer protein. It has been shown that blood pressure is related to insulin resistance independent of differences in age, gender, and degree of obesity (Zavaroni *et al.*, 1992; Ferrannini *et al.*, 1997).

The demonstration that insulin can stimulate endothelium dependent vasodilation, and that this is blunted in insulin resistant individuals, provides a plausible

mechanism to explain the elevation of blood pressure in the metabolic syndrome (Steinberg *et al.*, 1996). Evidence that insulin resistance underlies the metabolic syndrome is also provided by the fact that pharmacologic treatment with insulin-sensitizers (e.g., thiazolidinediones) can have beneficial effects not only on glucose and lipids, but also on blood pressure and on the inflammatory and pro-atherogenic derangements previously noted (Arner, 2003; Lyon *et al.*, 2003). Many suggest that visceral obesity is the primary determinant of insulin resistance and, as such, represents the fundamental pathophysiologic change leading to the metabolic syndrome (Kahn and Flier, 2000; Wajchenberg, 2000). Adipocyte-derived humoral factors that are released in proportion to visceral fat stores and that may mediate effects on insulin sensitivity include free fatty acids (FFAs), TNFα, IL-6, resistin, and others (Kahn and Flier, 2000; Dandona *et al.*, 2003). Perhaps the greatest support exists for FFAs, which have been shown to induce insulin resistance at both muscle and the liver (Kahn and Flier, 2000). Adiponectin is another "adipokine" of great interest. Levels of this polypeptide hormone fall with rising adiposity and adiponectin replacement has been shown to improve insulin sensitivity (Chandran *et al.*, 2003). The role of leptin in insulin resistance is unclear. Whereas some studies suggest that leptin may impair insulin action, leptin therapy dramatically improves insulin sensitivity in patients with lipodystrophy (Petersen *et al.*, 2002; Lyon *et al.*, 2003). Insulin resistance can also occur in lean individuals, which may be due to inherited insulin receptor and postreceptor defects (Hunter and Garvey, 1998). Despite this, the central role of visceral obesity in most cases of insulin resistance and the metabolic syndrome appears to be widely accepted.

A role of glucocorticoids in the pathogenesis of the metabolic syndrome is that cortisol excess can produce insulin resistance and the typical metabolic syndrome cluster is apparent from the clinical manifestation of Cushing's syndrome.

However, it has been proposed that "subclinical Cushing's syndrome" may be a relatively common cause of visceral obesity and the insulin resistance syndrome (Bjorntorp and Rosmond, 1999). Some of these cases may be due to functioning adrenal adenomas (Tauchmanova *et al.*, 2002), but physical stress or psychiatric stress have also been suggested as common causes of relative, and potentially relevant, hypercortisolaemia (Bjorntorp and Rosmond, 1999). This mechanism is especially attractive as an explanation for the higher prevalence of the metabolic syndrome and type 2 diabetes mellitus among patients with severe mental illness in the light of evidence for hypothalamic-pituitary-adrenal (HPA) axis overactivity and central adiposity.

2.13 METABOLIC SYNDROME AND PSYCHOTIC DISORDERS

Increasingly, physical disorders such as obesity, hyperlipidemias, hypertension, and type 2 diabetes mellitus are becoming recognized as significant comorbidities in people with serious mental illnesses, including psychotic disorders such as schizophrenia. Whether these disorders are part of the disease process itself through increased stress and inflammatory responses, genetic vulnerabilities, or environmental factors versus sequelae of treatment of the disease has been a matter of debate. Only recently have clinicians and researchers in the field of psychiatry begun to evaluate these comorbidities in the context of the metabolic syndrome.

The prevalence of being overweight or obese in individuals with schizophrenia has generally been thought to be greater than in individuals without the disorder (Gopalaswamy and Morgan, 1985). Allison and colleagues (1999) found that patients with schizophrenia tended to be as or more obese than the general population. Some obese individuals with large amounts of body fat display few metabolic complications, while in other individuals who appear minimally

overweight, the development of type 2 diabetes and cardiovascular diseases is increased (Bjorntorp, 1988; Bray, 1992).

Thakore et al (2002) have shown that increased visceral fat distribution was present in individuals with schizophrenia, independent of any medication effects. The group used abdominal computed tomography scanning in a cross-sectional study of 15 schizophrenic subjects who were either drug-free or drug-naive to measure fat distribution compared with a matched control group. While the schizophrenic subjects were found to have a nonsignificantly higher degree of total body fat and subcutaneous fat compared with controls, schizophrenic patients had 3.4 times as much intra-abdominal fat as did the normal controls. Visceral fat may be a common pathologic factor and may explain one reason why schizophrenic subjects are more likely to have an increased prevalence of metabolic complications associated with the metabolic syndrome. Several recent studies looked at whether patients with serious mental illness have an increased prevalence of the metabolic syndrome in comparison to the general population. As stated earlier, the current age-adjusted prevalence for the metabolic syndrome among the general population of U.S. adults is approximately 24% (Ford *et al.*, 2002). These data would support the suggestion by Reaven (2002) that increasing levels of insulin resistance are likely to be early predictors to the development of metabolic syndrome.

A study of metabolic syndrome within the Finnish general population (Vanhala *et al.*, 1997) demonstrated a prevalence ranging from 8% to 17%. Heiskanen et al (2003) have published a study examining the metabolic syndrome in 35 Finnish patients with schizophrenia and observed a 37% prevalence. This study showed higher rates of the metabolic syndrome among patients with schizophrenia

compared with background rates in the general population. The studies by Heiskanen et al. (2003) included an examination of antipsychotic medication treatment and failed to observe any significant differences in metabolic syndrome prevalence across typical and atypical antipsychotic treatment groups. These studies seem to indicate that a significant part of the risk for metabolic syndrome parameters is inherent in the psychiatric disease process itself and that antipsychotic medication may be an indirect factor in contributing to metabolic syndrome risk. However, these conclusions are limited by the studies' cross-sectional design and the relatively small sample sizes.

Rosmond & Bjorntorp (2000) have suggested that HPA axis dysregulation may also play a significant role in the development of various components of the metabolic syndrome. While increased cortisol production is a normal response to acute stress, several studies (Jakovljevic *et al.*, 1998; Thakore *et al.*, 2002; Ryan *et al.*, 2003; Thakore, 2005) have demonstrated a disruption in normal HPA axis activity and relative hypercortisolemia in patients with schizophrenia. Ryan et al. (Ryan *et al.*, 2003) have shown that first-episode treatment-naive patients with schizophrenia demonstrate a significantly higher plasma cortisol level along with a higher percentage of patients having impaired fasting glucose, increased fasting blood glucose levels, and increased insulin resistance compared with a matched control group. Chronic elevation in plasma cortisol levels can lead to a pseudo-Cushing's syndrome characterized by increased visceral adiposity, hyperinsulinemia, insulin resistance, dyslipidaemia and hypertension, all hallmarks of the metabolic syndrome (Ryan and Thakore, 2002). Shiloah et al. (2003) studied a group of 39 nondiabetic patients with acute psychotic stress admitted to an inpatient ward and examined the effects of the psychotic stress on glucose homeostasis. They demonstrated that patients undergoing an acute stress

situation necessitating psychiatric emergency ward admission had disruptions in beta-cell function and insulin sensitivity that correlated inversely with their degree of stress, suggesting that severity of illness may have an increased impact on HPA axis disruption.

2.14 ESSENTIAL FEATURES OF METABOLIC SYNDROME

Looking at the essential features of metabolic syndrome (abdominal obesity, hypertriglyceridaemia, low HDL-cholesterol and hypertension), current epidemiological data vary in their prevalence in different studies but the rates approximately range from 20-30% in majority of these studies. These figures increase as age advances and similarly different rates are reported for different gender, race and ethnicity (Lakka *et al.*, 2002; Kanauchi *et al.*, 2004). The National Health & Nutrition Examination Survey III, which was conducted among 8814 US adults aged at least 20 years, demonstrated that the percentage of individuals with at least one metabolic abnormality was 71%, at least two was 44% and at least three (meeting criteria for metabolic syndrome) was 24%. Nearly, 10% of individuals had at least four metabolic abnormalities and 3-5% had all components of the metabolic syndrome (St-Onge *et al.*, 2004). While recent reports are showing an increase of this syndrome among the general population, a growing concern is being expressed about this problem among mentally ill as well (Citrome *et al.*, 2005). It is an agreed fact that chronic mentally ill are more vulnerable for physical health problems and they show significant increase in relation to their physical health as compared to the general population (Phelan *et al.*, 2001; Ohlsen *et al.*, 2005). If we look at the risk factors contributing to the high prevalence of medical health problems in mentally ill, the presence of metabolic syndrome emerges as an important risk factor for cardiovascular and diabetic morbidity. It is generally

estimated that metabolic syndrome is especially common in patients with severe mental illnesses (SMI) with high prevalence in the range of 30-60% for schizophrenic and bipolar disorders (Ryan and Thakore, 2002; Thakore, 2005).

2.14.1 Diabetes and Severe Mental Illness

A number of publications have mentioned the potential relationship between antipsychotic drugs and hyperglycaemia (Sernyak *et al.*, 2002; Taylor *et al.*, 2005). The findings that first episode and drug naive patients may show insulin resistance complicates the underlying mechanisms in this regard (Ryan *et al.*, 2003). Worsening of glucose control may not be explained exclusively on the individual drugs itself but the contribution of these drugs for other components of metabolic syndrome including cardiovascular risks and dyslipidaemia certainly contribute to such predisposition (Jin *et al.*, 2004). Three retrospective chart reviews (Lilliker, 1980; Regenold *et al.*, 2002) in psychiatric settings have found that patients with bipolar disorder have an increased prevalence of diabetes compared with the general population. In addition, there is some evidence (Gildea *et al.*, 1943; Ruzickova *et al.*, 2003) that patients with bipolar disorder have abnormalities in oral glucose tolerance test. Two of these studies Regenold et al., (2002) and Ruzickova et al., (2003) examining the possible association of medication effects found no significant relation between antipsychotic use and diabetes. Recent literature is again consistent about the prevalence rate of diabetics ie. around 15% in populations with schizophrenia, which represents a two to threefold increase in risk compared to the general population (Kohen, 2004; Susce *et al.*, 2005).

2.14.2 Antipsychotic Medication and Weight Gain

Weight gain is an established side effect of most of the antipsychotic drugs (including typical and atypical antipsychotics). This association is well

documented for the first generation typical antipsychotics (as for back as 1960) and more recently same association has been described for the newer or second generation atypical antipsychotic drugs (Klett and Caffey, 1960; Taylor and McAskill, 2000). Many underlying mechanisms operate in weight gain after intake of these drugs. Genetic variation may also play a role (Gough and O'Donovan, 2005) and though the underlying mechanism remains uncertain, most of these drugs increase weight primarily by increasing caloric intake leading to an increase in adiposity. Excessive weight gain has many adverse clinical consequences including predisposition to a number of physical illnesses like cardiovascular disorders, diabetes, stroke, osteoarthritis and sleep apnoea in addition to low self esteem, decreased quality of life and reduced adherence to treatment. The weight changes has been associated with almost all antipsychotic drugs & this has been consistently observed in clinical experiences both in naturalistic studies as well as in short term & long term Randomized Control Trials (RCTs) (Klett and Caffey, 1960; Taylor and McAskill, 2000). Although current clinical trials and evidence point towards an increase in weight after use of all the conventional and atypical antipsychotics but among the atypicals mean weight gain is greatest with olanzapine and clozapine and least with Aripeprazole and Ziprasidone (McIntyre *et al.*, 2003; Smith *et al.*, 2005). This has important clinical implications in that it exposes these patients to the risk associated with weight gain such as obesity, hypertension, coronary heart disease and many other physical problems. It is important to know that the mentally ill are already at risk of higher standardized mortality rate and this particular side effect of the prescribed medication certainly pose more disadvantages. It is still unclear whether antipsychotics affect glucose metabolism directly or increase the weight by insulin resistance or work through social disadvantages or some other mechanism (Bushe and Leonard, 2004). Given the growing epidemic of obesity and its consequences, the weight changes in the

mentally ill taking antipsychotic medication however remains increasingly relevant.

2.14.3 Antipsychotic Medication and Adverse Lipid Levels

The links between antipsychotic medication and adverse lipid levels is also worth noting. During the last few decades, reports have appeared in the medical literature showing an increase in cholesterol and triglycerides in patients taking typical antipsychotics (Shafique *et al.*, 1988). A number of reports have also shown the comparative effects of atypical antipsychotics on lipid levels and other reports (Meyer, 2001; Paton *et al.*, 2004) have demonstrated between atypical antipsychotic medication and impaired glucose tolerance and changes in lipids profiles strengthen these views. Poor diet, lack of exercise and increased body weight that are common in the mentally ill, are all major predisposing factors for these changes. Majority of these studies are short term and regular monitoring of lipids is not taking place routinely at many centres. But despite these methodological shortcomings in these studies, the concern continues to be of high magnitude (Lambert *et al.*, 2005).

The main lipids present in serum are cholesterol and triglycerides and their measurement is therefore essential in individuals who are vulnerable for cardiovascular diseases or type 2 diabetes (Mokdad *et al.*, 2003). Elevated levels of lipids may be attributed to a combination of life style, genetic and many other factors but evidence is accumulating that lipid values above the optimal maximum are observed in many patients who suffer from severe mental illnesses. In terms of lipids profiles in mentally ill, although there is a paucity of data, but there are reports available that shows an increased prevalence of elevated lipid levels or at least the same extent as in the most vulnerable general population. The recent

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study that involved a large sample of schizophrenic patients showed that 64% of subjects met criteria for hyperlipidemia (Stroup *et al.,* 2003). Similarly a Finish study reported that individuals treated with antipsychotic medications were three times more likely to have high cholesterol or high triglyceride than those who were not taking these drugs (Saari *et al.,* 2004).

Chapter 3

MATERIALS AND METHODS

3.1 STUDY POPULATION AND SETTING

A total of 200 psychiatric patients comprising 100 newly diagnosed antipsychotic naïve patients and 100 patients on antipsychotic medication visiting the psychiatric department of the Komfo Anokye Teaching Hospital (KATH) were recruited for this study. Ethical clearance and approval for the study was given by the Committee on Human Research, Publications and Ethics, Kwame Nkrumah University of Science and Technology, School of Medical Sciences & KATH, Kumasi, Ghana.

3.2 SAMPLING

About 5 ml of venous blood sample was collected from the antecubital fossa of the study participants after an overnight fast (12 – 16 hours). One (1 ml) of the blood sample was dispensed into fluoride oxalate tube and the other 4 ml into vacutainer plain tubes. Serum and plasma were stored at -80^{0}C after centrifugation at 500 *g* for 15 minutes until assay was performed. Assay parameters include: fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) cholesterol and uric acid. Serum low density lipoprotein (LDL) cholesterol was estimated from the Friedewald equation. The assay was performed on the biochemistry autoanalyzer, Roche COBAS Integra® 400 Plus System (Roche Diagnostics, Germany, West Berlin) with the system's respective reagent cassettes. Malondialdehyde (MDA) concentration was determined by the method described by Kamal *et al.*, (1989).

3.3 ASSAY PROCEDURES

3.3.1 Fasting Blood Glucose

Glucose concentration in the samples was estimated with the hexokinase method. Hexokinase (HK) phosphorylates glucose with ATP to produce glucose-6-phosphate, which is then oxidized by glucose-6-phosphate dehydrogenase to 6-phosphogluconate with the simultaneous reduction of NAD^+ to NADH. The resulting increase in absorbance at 340nm is directly related to the concentration of glucose in the sample.

$$Glucose + ATP \xrightarrow{HK} Glucose - 6 - phosphate + ADP$$

$$Glucose - 6 - phosphate + NAD^+ \xrightarrow{G6PDH} Phosphogluconate + NADH$$

3.3.2 Total Cholesterol

The method for this assay is based on that described by Trinder, (1969). Cholesterol esterase hydrolyses esters to free cholesterol and fatty acids. The free cholesterol produced plus the preformed cholesterol are then oxidized in the presence of cholesterol oxidase to cholest-4-en-3-one and hydrogen peroxide. The quinoneimine chromogen, with absorption maximum at 500 nm, is produced when phenol is oxidatively coupled with 4-aminophenazone in the presence of peroxidase with hydrogen peroxide. The intensity of the final red colour is directly proportional to the total cholesterol concentration.

$$Cholesterol + H_2O \xrightarrow{cholesterol\ esterase} Cholesterol + Fatty\ acids$$

$$Cholesterol + O_2 \xrightarrow{cholesterol\ oxidase} Cholest - 4 - en - 3 - one + H_2O_2$$

$$H_2O_2 + 4 - aminophenazone + Phenol \xrightarrow{peroxidase} H_2O + Quinoneimine$$

3.3.3 Triglycerides

The method for this assay is based on a modified Trinder (Barham and Trinder, 1972) colour reaction to produce a fast linear endpoint reaction (McGowan *et al.*, 1983). Triglycerides in the sample are hydrolyzed by lipase to glycerol and fatty acids. Glycerol is then phosphorylated by adenosine-5-triphosphate (ATP) to glycerol-3-phosphate and adenosine-5-diphosphate (ADP) in a reaction catalyzed by glycerol kinase. Glycerol-3-phosphate is then converted to dihydroxyacetone phosphate (DHAP) and hydrogen peroxide (H_2O_2) by glycerophosphate oxidase. The hydrogen peroxide the reacts with 4-aminoantipyrine and 3, 5 dichloro-2-hydroxybenzene (Chlorophenol) in a reaction catalyzed by peroxidase to yield a red coloured quinoneimine dye. The intensity of the colour produced is directly proportional to the concentration of triglycerides in the sample.

$$Triglyceride + H_2O \xrightarrow{lipase} Glycerol + Fatty\ acids$$

$$Glycerol + ATP \xrightarrow{glycerol\ kinase} Glyerol - 3 - phosphate + ADP$$

$$Glycerol - 3 - phosphate \xrightarrow{glycerophosphate\ oxidase} DHAP + H_2O_2$$

$$2H_2O_2 + 4 - aminoantipyrine + chlorophenol \xrightarrow{peroxidase} Quinoneimine + 2H_2O$$

3.3.4 HDL Cholesterol

Low density lipoproteins (LDL and VLDL) and chylomicron fractions are precipitated quantitatively by the addition of phosphotungstic acid in the presence of Mg2+ ions. The cholesterol concentration in the HDL is then determined by the method described by Trinder for the assay of cholesterol.

3.3.5 LDL Cholesterol

The LDL-Cholesterol concentration (LDL-C) is calculated from the total cholesterol concentration (TC), HDL-Cholesterol concentration (HDL-C) and the triglycerides concentration (TG) according to Friedewald equation (Friedewald *et al.*, 1972).

$$LDL - Cholesterol(mmol\ L^{-1}) = TC(mmol\ L^{-1}) - \frac{TG(mmol\ L^{-1})}{2.2} - HDL(mmol\ L^{-1})$$

3.3.6 Uric Acid

Uric acid is converted by oxidation by uricase to allantoin and H_2O_2, which under the catalytic influence of peroxidase, oxidizes 3, 5-dichloro-2-hydroxybenzene-sulphonic acid (chlorophenol sulphonic acid) and 4-aminophenazone (4AP) to form a red-violet quinonimine compound, which is proportional to the amount of uric acid present.

$$Uric\ acid + O_2 + 2H_2O_2 \xrightarrow{uricase} Allantoin + CO_2 + H_2O_2$$

$$2H_2O_2 + chlorophenol\ sulphonic\ acid + 4AP \xrightarrow{peroxidase} N-(4-antipyryl) - 3-chloro-5-sulphonate-p-benzo-quinoneimine$$

3.3.7 Malondialdehyde (MDA)

The method used for this assay was based on that of Kamal *et al.*, (1989). A volume of 0.5 ml of serum was treated with 2.5 ml of 20% trichloroacetic acid (TCA) and then 1 ml of 0.67% TBA. The mixture was incubated at 100°C for 30 minutes. After cooling, the sample was extracted with 4 ml n-butanol and centrifuged at 500 *g* for 10 min. The absorbances of supernatant were measured at 535 nm and the results were expressed as µmol L^{-1}, using the extinction coefficient of 1.56 x 10^5 L mmol cm^{-1}.

3.4 ANTHROPOMETRIC VARIABLES

Height to the nearest centimetre without shoes was measured against a wall-mounted ruler and weight to the nearest 0.1 kg in light clothing on a bathroom scale (Zhongshan Camry Electronics Co. Ltd. Guangdong, China). The body mass index (BMI) was calculated by dividing weight (kg) over the height squared (m^2). Waist circumference (to the nearest centimetre) was measured with a Gulick II spring-loaded measuring tape (Gay Mill, WI) midway 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).

3.5 DEFINITIONS FOR METABOLIC SYNDROME

Three of the competing definitions of metabolic syndrome generally referred to in medical writings used in this study are as follows:

3.5.1 National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) Criteria:

The NCEP ATP III criteria mandates that individuals with metabolic syndrome should have three or more of the following five components of metabolic syndrome: (1) Abdominal obesity (waist circumference >102 cm for men or >88 cm for women); (2) Raised triglyceride (≥1.7 mmol L^{-1}); (3) Low HDL-cholesterol (<0.9 mmol L^{-1} in men or <1.0 mmol L^{-1} in women); (4) High Blood Pressure (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or treatment of hypertension) and (5) Raised fasting glucose (≥6.1 mmol L^{-1}) (NCEP, 2002).

3.5.2 International Diabetes Federation (IDF) Criteria

The IDF criteria mandates that metabolic syndrome be diagnosed if Central obesity (waist circumference >90 cm for men or >80 cm for women) is accompanied by any two (2) of the following four (4) factors: (1) Triglyceride level ≥1.7 mmol L^{-1}; (2) HDL cholesterol <1.03 mmol L^{-1} for men or <1.29 mmol L^{-1} for women; (3) Blood pressure ≥130/85 mmHg or treatment of previously diagnosed hypertension and (4) Fasting blood glucose (FBG) ≥5.6 mmol L^{-1} or previously diagnosed type 2 diabetes (Alberti *et al.*, 2006).

3.5.3 World Health Organization (WHO) Criteria

The WHO criteria mandates the presence of diabetes mellitus, impaired glucose tolerance or insulin resistance and any two (2) of the following: (1) Body mass index (BMI) ≥30 kg m^{-2} and/or waist to hip ratio >0.90 for males or >0.85 for females; (2) Blood pressure ≥140/90 mmHg or on medication; (3) Triglyceride ≥1.7 mmol L^{-1} and (4) HDL cholesterol <0.91 mmol L^{-1} in males or <1.01 mmol L^{-1} in females (World Health Organization, 1999).

3.6 STATISTICAL ANALYSIS

Results are presented as Means ± SEM. Unpaired *t*-test was used to compare the means of all continuous variables. The Chi-square test statistic was used to assess the statistical significance of categorical variables. Odds analysis and confidence intervals of metabolic syndrome was done using the Odds ratio test statistic. Logistic regression test statistic was used to estimate the crude (c) and adjusted (adj) odds ratio (OR) for risk factors of metabolic syndrome. A p-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using MedCalc® version 10.2.0.0 (www.medcalc.be) for windows.

Chapter 4

RESULTS

4.1 GENERAL CHARACTERISTICS

Table 4.1 presents the general characteristics of the study population stratified by treatment. Patients on treatment were significantly older (37.86 ± 1.36 years) and heavier (66.10 ± 1.36 kg) than the newly diagnosed patients (26.17 ± 1.02 years and 61.93 ± 1.30 kg respectively) to weight and to age. The mean waist circumference in patients on treatment (85.17 ± 1.26 cm) as a marker of central obesity was significantly higher compared to the newly diagnosed patients (76.72 ± 0.97 cm) ($p < 0.0001$) likewise the body mass index of 24.73 ± 0.54 kg m^{-2} and 22.66 ± 0.57 kg m^{-2} respectively ($p = 0.0088$). The mean systolic (125.20 ± 1.99 mmHg) and diastolic (79.53 ± 1.01 mmHg) blood pressure in patients on treatment was also significantly higher in comparison to the newly diagnosed patients (117.80 ± 1.78 mmHg, 75.30 ± 0.90 mmHg respectively) ($p = 0.0063$ and 0.0020 respectively).

The mean concentration of the lipid profile components of total cholesterol (4.74 ± 0.12 mmol L^{-1}), low density lipoprotein cholesterol (2.90 ± 0.09 mmol L^{-1}) and very low density lipoprotein (0.29 ± 0.01 mmol L^{-1}) in patients on treatment ($p = 0.0028$, <0.0001 and 0.0116 respectively) was significantly higher than in newly diagnosed patients with mean concentrations of (4.30 ± 0.08, 2.36 ± 0.08 and 0.24 ± 0.01 mmol L^{-1} respectively). Conversely, the mean concentrations of high density lipoprotein (1.19 ± 0.04 mmol L^{-1}, $p = 0.0007$) and MDA (0.83 ± 0.02 mmol L^{-1}, $p < 0.0001$) in patients on treatment were significantly lower compared to that in newly diagnosed patients (1.35 ± 0.03 mmol L^{-1} and 0.93 ± 0.01 respectively) while the mean triglyceride, fasting blood glucose concentrations and waist to hip ratio showed no statistically significant differences.

Table 4.1 General characteristics of the study population stratified by treatment

Variables	Total *(n = 200)*	On Treatment *(n = 100)*	Newly Diagnosed *(n = 100)*	P value
Age (yrs)	32.02 ± 0.94	37.86 ± 1.36	26.17 ± 1.02	< 0.0001
Weight (kg)	64.02 ± 0.95	66.10 ± 1.36	61.93 ± 1.30	0.0277
Height (m)	1.65 ± 0.01	1.64 ± 0.01	1.67 ± 0.01	0.0538
WC (cm)	81.22 ± 0.86	85.71 ± 1.26	76.72 ± 0.97	<0.0001
HC (cm)	98.70 ± 0.90	100.30 ± 1.41	97.08 ± 1.12	0.0727
WHR	1.05 ± 0.23	1.31 ± 0.47	0.79 ± 0.01	0.2683
BMI (kg m^{-2})	23.70 ± 0.40	24.73 ± 0.54	22.66 ± 0.57	0.0088
SBP (mmHg)	121.50 ± 1.36	125.20 ± 1.99	117.80 ± 1.78	0.0063
DBP (mmHg)	77.42 ± 0.69	79.53 ± 1.01	75.30 ± 0.90	0.0020
FBS (mmol L^{-1})	5.37 ± 0.15	5.49 ± 0.25	5.25 ± 0.15	0.4262
Uric acid (μmol L^{-1})	236.30 ± 5.09	255.30 ± 7.94	217.40 ± 5.79	0.0002
TC (mmol L^{-1})	4.52 ± 0.07	4.74 ± 0.12	4.30 ± 0.08	0.0028
TG (mmol L^{-1})	1.35 ± 0.05	1.42 ± 0.07	1.28 ± 0.06	0.1384
HDL-C (mmol L^{-1})	1.27 ± 0.02	1.19 ± 0.04	1.35 ± 0.03	0.0007
LDL-C (mmol L^{-1})	2.63 ± 0.06	2.90 ± 0.09	2.36 ± 0.08	<0.0001
VLDL (mmol L^{-1})	0.26 ± 0.01	0.29 ± 0.01	0.24 ± 0.01	0.0116
MDA (μmol L^{-1})	0.88 ± 0.01	0.83 ± 0.02	0.93 ± 0.01	<0.0001

Results are presented as mean ± SEM. P value defines the level of significance when study population on treatment was compared to the newly diagnosed. WC = waist circumference, HC = hip circumference, WHR = waist to hip ratio, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, FBS = fasting blood glucose, TC = total cholesterol, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, VLDL = very low density lipoprotein, MDA = malondialdehyde.

4.2 CO-MORBID CONDITIONS

Odds analysis to evaluate the risk of developing certain physical co-morbidities and lifestyle associated with metabolic syndrome in psychiatrics based on treatment are shown in Table 4.2. Patients on treatment are approximately 12 times at risk of indulging in alcoholism (p =0.0235) and 26 times at risk of developing hyperuricaemia (p = 0.0007) when compared to the newly diagnosed patients. The odds of being obese (2.5 times), developing hypercholesterolaemia (3 times),

having low high density lipoprotein (HDL) cholesterol (3 times), developing high low density lipoprotein (LDL) cholesterol (3 times) in patients on treatment were statistically significant compared to the newly diagnosed patients. Being on treatment confers some level of protection against oxidative stress ($p = 0.0097$) while gender, smoking, hypertension, diabetes and hypertriglyceridaemia showed no statistical significance when patients on treatment were compared to the newly diagnosed patients.

4.3 PREVALENCE OF METABOLIC SYNDROME

Table 4.3 presents a general overview of the metabolic syndrome score in the study population defined by three different classification criteria. When defined by the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) criteria, 21.0% of the patients on treatment compared to 2.0% of the newly diagnosed patients had metabolic syndrome (score ≥ 3) with an odds ratio of 13.0 ($p < 0.0001$). In using the International Diabetic Federation (IDF) criteria, 29.0% of the patients on treatment compared to 2.0% of the newly diagnosed patients had developing metabolic syndrome (OR = 20.0, $p < 0.0001$). Contrary to the results from the two criteria stated above, the World Health Organization (WHO) criteria gave percentage prevalence of 13.0% and 14.0% in patients on treatment and newly diagnosed patients respectively with an odds ratio of 0.9 but the difference was not statistically significant ($p = 0.8372$) (Figure 4.1). Pearson's correlation analysis between age and metabolic syndrome defined by NCEP ATP III ($r = 0.363$, $p = <0.0001$); WHO ($r = 0.190$, $p = <0.01$) and IDF ($r = 0.469$, $p = <0.0001$) criteria showed significant positive linear relationship between increasing age and the risk for metabolic syndrome.

Table 4.2 Co-morbid conditions stratified by treatment among the studied population

Variables	Total (*n = 200*)	On Treatment (*n = 100*)	Newly Diagnosed *(n = 100)*	OR(95% CI)	P value
Females	121(60.5%)	63(63.0%)	58(58.0%)	1.2(0.7-2.2)	0.5630
Smokers	1(0.5%)	1(1.0%)	0(0.0%)	3.0(0.1-75.3)	1.0000
Alcohol	5(2.5%)	5(5.0%)	0(0.0%)	11.6(0.6-212.3)	0.0235
Hypertension	28(14.0%)	17(17.0%)	11(11.0%)	1.7(0.7-3.7)	0.3083
Diabetes	53(26.5%)	27(27.0%)	26(26.0%)	1.1(0.6-2.0)	1.0000
Obesity	33(16.5%)	16(16.0%)	7(7.0%)	2.5(1.0-6.5)	0.0461
Hypercholesterolaemia	43(21.5%)	30(30.0%)	13(13.0%)	2.9(11.4-5.9)	0.0055
Hypertriglycerideamia	58(29.0%)	28(28.0%)	30(30.0%)	0.9(0.5-1.7)	0.8763
Low HDL-Cholesterol	51(25.5%)	36(36.0%)	15(15.0%)	3.2(1.6-6.3)	0.0011
High LDL-cholesterol	168(84.0%)	91(91.0%)	77(77.0%)	3.0(1.3-6.9)	0.0113
Hyperuricaemia	11(5.5%)	11(11.0%)	0(0.0%)	25.8(1.5-444.9)	0.0007
Oxidative stress	189(94.5%)	90(90.0%)	99(99.0%)	0.1(0.0-0.7)	0.0097

Obesity is defined as BMI ≥ 30 kg m^{-2}, Hypertension = blood pressure ≥ 140/90 mmHg, Diabetes = fasting blood glucose greater or equal to 7.0 mmol L^{-1}, Hypercholesterolaemia = total cholesterol > 5.2 mmol L^{-1}, Hypertriglyceridaemia = triglyceride > 1.8 mmol L^{-1}, Low HDL-Cholesterol = HDL-C < 1.0 mmol L^{-1}, High LDL-cholesterol = LDL-C > 1.8 mmol L^{-1}, and Hyperuricaemia = uric acid > 416.4 µmol L^{-1} (for men) and 356.9 µmol L^{-1} (for women), oxidative stress = MDA > 0.7 µmol L^{-1}.

Table 4.3 Prevalence of metabolic syndrome and its score among the studied population stratified by treatment

Variables	Total (*n=200*)	On Treament (*n =100*)	Newly Diagnosed (*n= 100*)	OR(95% CI)	P value
National Cholesterol Education Programme Adult Treatment Panel III criteria					
MetS Score/Age correlation		R = 0.363			<0.0001
0	52(26.0%)	19(19.0%)	33(33.0%)	0.5(0.3-1.0)	0.0560
1	81(40.5%)	34(34.0%)	47(47.0%)	0.6(0.3-1.0)	0.0611
2	44(22.0%)	26(26.0%)	18(18.0%)	1.8(0.9-3.5)	0.0866
≥3	23(11.5%)	21(21.0%)	2(2.0%)	13.0(3.0-57.3)	< 0.0001
World Health Organization criteria					
MetS Score/Age correlation		R = 0.190			<0.0010
0	102(51.0%	42(42.0%)	60(60.0%)	0.5(0.3-0.8)	0.0109
1	47(23.5%)	24(24.0%)	23(23.0%)	1.1(0.6-2.0)	0.8693
2	22(11.0%)	19(19.0%)	3(3.0%)	7.6(2.2-76.6)	0.0003
≥3	19(9.5%)	15(15.0%)	4(4.0%)	4.2(1.4-13.3)	0.0080
International Diabetic Federation criteria					
MetS Score/Age correlation		R = 0.469			<0.0001
0	58(29.0%)	22(22.0%)	36(36.0%)	0.5(0.3-0.9)	0.0291
1	70(35.0%)	32(32.0%)	38(38.0%)	0.8(0.4-1.4)	0.3737
2	50(25.0%)	26(26.0%)	24(24.0%)	1.1(0.6-2.1)	0.7440
≥3	22(11.0%)	20(20.0%)	2(2.0%)	12.3(2.8-54.0)	<0.0001

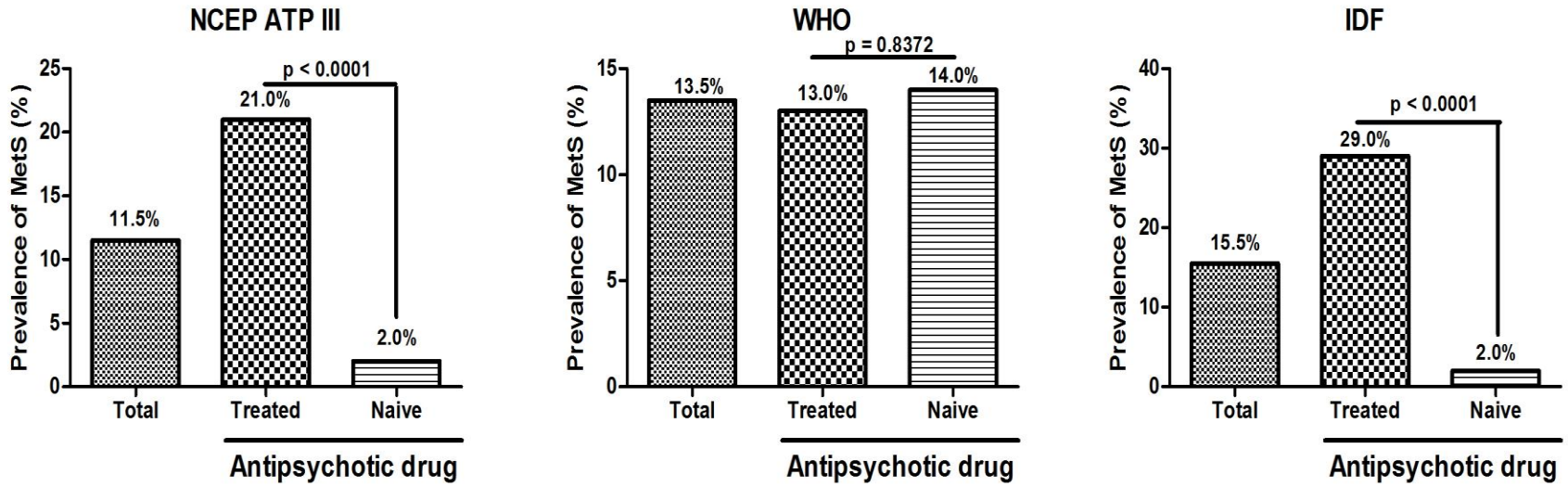

Figure 4.1 Prevalence of metabolic syndrome stratified by treatment with antipsychotic

4.4 PREVALENCE OF COMPONENTS OF METABOLIC SYNDROME

Assessment of the percentage prevalence of the individual components of metabolic syndrome per the classification criteria for the study population is presented in Table 4.4. Patients on treatment are more prone to being obese when classified by the NCEP ATP III, IDF and WHO criteria with percentage prevalence of 32.0% ($p = 0.0006$), 47.0% ($p < 0.0001$) and 40.0% ($p = 0.0149$) respectively. Twenty-three percent (23%) of the patients on treatment are more likely to develop significantly raised blood pressure compared to 11.0% of the newly diagnosed patients when classified by the NCEP ATP III and IDF criteria ($p = 0.0384$). However, no statistically significant difference was observed when raised blood pressure was assessed in patients on treatment and newly diagnosed patients with the WHO criteria ($p = 0.3082$). No significant difference in the prevalence of raised fasting blood glucose was observed in the study population when evaluated with the three classification criteria and likewise in the prevalence of raised triglyceride levels. The prevalence of low HDL cholesterol in patients on treatment as determined by the NCEP ATP III and WHO criteria showed no statistical significance but when classified by the IDF criteria, 50.0% of the patients on treatment are at risk of developing reduced HDL levels compared to 11.0% in newly diagnosed patients and the difference was statistically significant.

4.5 RISK FACTORS OF METABOLIC SYNDROME

Table 4.5 shows univariate analysis of the risk factors of metabolic syndrome evaluated by the three classification criteria for the study population. When classified by logistic regression with NCEP ATP III criteria as the dependent variable, treatment (cOR = 13.0, $p = 0.001$), obesity-WC[1] (cOR = 3.2, $p = 0.011$), obesity-WC[2] (cOR = 2.6, $p = 0.037$), obesity BMI (cOR = 1.8, $p = 0.026$), raised BP[1] (cOR = 3.1, $p = 0.020$), hyperuricaemia (cOR = 5.1, $p = 0.015$), hypercholesterolaemia (cOR = 2.5, $p = 0.048$) and raised TG (cOR = 3.1, $p = 0.012$)

turned out to be significant risk variables and predictors of metabolic syndrome. However, when the risk variables were further assessed with adjustment for age

Table 4.4 Prevalence of metabolic syndrome components among the study populations stratified by treatment

Parameters	Total *(n = 200)*	On Treatment *(n = 100)*	Newly Diagnosed *(n = 100)*	P value
OBESITY				
NCEP ATP III Criteria				
> 102 cm (men)/> 88 (women)	43 (21.5%)	32 (32.0%)	11 (11.0%)	0.0006
IDF Criteria				
> 90 (men)/> 80 (women)	64 (32.0)	47 (47.0%)	17 (17.0%)	< 0.0001
WHO Criteria				
> 0.9 (men)/> 0.85 (women)	63 (31.5)	40 (40.0%)	23 (23.0%)	0.0149
BLOOD PRESSURE				
NCEP ATP III/IDF Criteria				
≥ 130/85	34 (17.0)	23 (23.0%)	11 (11.0%)	0.0384
WHO Criteria				
≥ 140/90	28 (14.0%)	17 (17.0%)	11 (11.0%)	0.3082
FASTING BLOOD GLUCOSE				
NCEP ATP III/WHO Criteria				
≥ 6.1	55 (27.5%)	29 (29.0%)	26 (26.0%)	0.7515
IDF Criteria				
≥ 5.6	57 (28.5%)	31 (31.0%)	26 (26.0%)	0.5309
TRIGLYCERIDE				
≥ 1.7	58 (29.0%)	28 (28.0%)	30 (30.0%)	0.8762
HDL-C				
NCEP ATP III/WHO Criteria				
< 0.9 (men)/< 1.0 (women)	36 (18.0%)	23 (23.0%)	13 (13.0%)	0.0976
IDF Criteria				
< 1.03 (men)/< 1.29 (women)	61 (30.5%)	50 (50.0%)	11 (11.0%)	< 0.0001

NCEP ATP III = National Cholesterol Education Program, Adult Treatment Panel III, IDF = International Diabetes Federation, WHO = World Health Organization, HDL-C = High Density Lipoprotein Cholesterol.

Table 4.5 Univariate analysis of risk factors for metabolic syndrome among the study population (N = 200)

	NCEP ATP III		WHO		IDF	
Variables	**cOR(95% CI)**	**P value**	**cOR(95% CI)**	**P value**	**cOR(95% CI)**	**P value**
Female	2.0(0.7-5.3)	0.168	1.7(0.7-4.0)	0.263	2.5(1.0-6.2)	0.041
Treatment	13.0(3.0-57.2)	0.001	0.9(0.4-2.1)	0.836	20.0(4.6-86.6)	0.000
Obesity-WC[1]	3.2(1.3-8.0)	0.011	1.0(0.4-2.7)	0.976	3.8(1.7-8.6)	0.001
Obesity-WC[2]	2.6(1.1-6.1)	0.037	0.9(0.4-2.1)	0.732	3.6(1.6-7.9)	0.001
Obesity-WHR	1.4(0.6-3.6)	0.443	1.6(0.7-3.8)	0.264	1.8(0.8-4.0)	0.152
Obesity-BMI	1.8(1.2-9.6)	0.026	0.6(0.1-2.6)	0.478	2.1(0.8-6.0)	0.143
Raised BP[1]	3.1(1.2-8.0)	0.020	1.5(0.5-4.0)	0.440	1.9(0.8-4.7)	0.161
Raised BP[2]	1.9(0.6-5.5)	0.262	1.5(0.5-4.3)	0.469	1.6(0.6-4.3)	0.353
Raised FBS[1]	1.5(0.6-3.7)	0.408	1.4(0.5-3.3)	0.467	0.9(0.4-2.2)	0.818
Raised FBS[2]	1.4(0.6-3.5)	0.479	1.3(0.5-3.1)	0.551	0.9(0.4-2.0)	0.718
Hyperuricaemia	5.1(1.4-19.1)	0.015	0.6(0.1-5.1)	0.663	2.2(0.5-8.6)	0.277
Hypercholesterolaemia	2.5(1.0-6.3)	0.048	1.2(0.5-3.2)	0.647	1.8(0.8-4.2)	0.161
Raised TG	3.1(1.3-7.5)	0.012	1.8(0.8-4.3)	0.152	1.4(0.6-3.2)	0.388
Reduced HDL-C[1]	1.7(0.6-4.7)	0.288	1.4(0.5-3.7)	0.540	1.8(0.7-4.3)	0.223
Reduced HDL-C[2]	1.7(0.7-4.1)	0.236	1.0(0.4-2.5)	0.921	2.6(1.2-5.7)	0.016
High LDL-C	2.1(0.5-9.6)	0.320	0.8(0.3-2.3)	0.702	1.3(0.4-4.1)	0.610
Oxidative stress	0.6(0.1-5.7)	0.689	0.8(0.1-6.9)	0.818	0.2(0.0-0.9)	0.034

Obesity-WC[1] = NCEP ATP III criteria, Obesity-WC[2] = IDF criteria, Raised BP[1] = NCEP ATP III/IDF criteria, Raised BP[2] = WHO criteria, Raised FBS[1] = NCEP ATP III/WHO criteria, Raised FBS[2] = IDF criteria, Reduced HDL-C[1] = NCEP ATP III/WHO criteria, Reduced HDL-C[2] = IDF criteria, cOR = crude odds ratio, CI = confidence interval.

(Table 4.6), only treatment (adjOR = 6.8, p = 0.015), obesity-WC[1] (adjOR = 2.5, p = 0.048), obesity BMI (adjOR = 4.8, p = 0.009) and raised TG (adjOR = 4.4, p = 0.004) turned out as true significant predictor variables for metabolic syndrome when classified by the NCEP ATP III criteria.

When the IDF criteria was applied, female sex (cOR = 2.5, p = 0.041), treatment (cOR = 20.0, p < 0.001), obesity-WC[1] (cOR = 3.8, p = 0.001), obesity-WC[2] (cOR = 3.6, p = 0.001) and reduced HDL-C[2] (cOR = 2.6, p = 0.016) were significant risk variables and predictors of metabolic syndrome with the exception of oxidative stress (cOR = 0.2, p = 0.034) which appeared to confer some level of protection against the development of metabolic syndrome. Upon adjusting for age, the above mentioned risk variables turned out as true significant predictors of metabolic syndrome in addition to obesity BMI (adjOR = 3.1, p = 0.045) with adjusted odds ratio of 2.9, 9.5, 3.3, 3.2 and 2.3 respectively. Furthermore, oxidative stress turned to be a significant protector from the development of metabolic syndrome (Tables 4.5 & 4.6).

No statistically significant differences were observed in the risk variables when classified by the WHO criteria in both univariate analyses and age-adjusted analyses (Tables 4.5 & 4.6).

Table 4.6 Age adjusted odds ratio of the risk factors for metabolic syndrome among the study population (N = 200)

	ATP III		WHO		IDF	
Variables	**adjOR(95% CI)**	**P value**	**adjOR(95% CI)**	**P value**	**adjOR(95% CI)**	**P value**
Female	1.9(0.7-5.5)	0.216	1.6(0.7-4.0)	0.292	2.9(1.0-7.8)	0.041
Treatment	6.8(1.5-31.4)	0.015	0.5(0.2-1.3)	0.137	9.5(2.1-43.2)	0.003
Obesity WC[1]	2.5(1.0-6.8)	0.048	0.8(0.3-2.3)	0.697	3.3(1.3-8.5)	0.014
Obesity WC[2]	2.0(0.8-5.3)	0.140	0.7(0.3-1.8)	0.451	3.2(1.3-8.0)	0.011
Obesity WHR	1.0(0.3-2.7)	0.940	1.4(0.6-3.3)	0.463	1.2(0.5-3.1)	0.720
Obesity BMI	4.8(1.5-15.4)	0.009	0.6(0.1-2.7)	0.500	3.1(1.0-10.0)	0.045
Raised BP[1]	1.9(0.6-5.5)	0.250	1.1(0.4-3.1)	0.860	0.9(0.3-2.7)	0.803
Raised BP[2]	1.0(0.3-3.6)	0.960	1.1(0.4-3.5)	0.815	0.7(0.2-2.6)	0.632
Raised FBS[1]	1.9(0.7-5.2)	0.223	1.5(0.6-3.7)	0.354	1.1(0.4-2.9)	0.889
Raised FBS[2]	1.8(0.7-5.1)	0.238	1.5(0.6-3.6)	0.399	1.1(0.4-2.9)	0.914
Hyperuricaemia	3.2(0.8-13.6)	0.108	0.4(0.1-3.6)	0.437	1.0(0.2-4.7)	0.984
Hypercholesterolaemia	2.0(0.7-5.3)	0.183	1.0(0.4-2.7)	0.957	1.3(0.5-3.3)	0.641
Raised TG	4.4(1.6-12.1)	0.004	2.0(0.8-4.7)	0.114	1.8(0.7-4.7)	0.223
Reduced HDL[1]	1.9(0.6-5.6)	0.273	1.4(0.5-3.7)	0.554	2.0(0.7-5.9)	0.184
Reduced HDL[2]	1.3(0.5-3.4)	0.600	0.9(0.4-2.2)	0.785	2.3(1.0-5.6)	0.043
High LDL-C	1.9(0.4-5.6)	0.422	0.7(0.3-2.2)	0.582	1.1(0.3-3.8)	0.921
Oxidative stress	0.6(0.1-6.0)	0.655	0.8(0.1-7.2)	0.834	0.1(0.0-0.7)	0.018

adjOR = adjusted odds ratio

4.6 STRATIFICATION BY TYPE OF TREATMENT

The results of patients on treatment further classified into two categories, conventional and atypical based on the composition of drug regimen are presented in Table 4.7. The mean age, weight, waist circumference, waist to hip ratio, body mass index, low density lipoprotein (LDL) cholesterol and malondialdehyde (MDA) values in the conventional treatment group were not significantly different from that in the atypical treatment group ($p > 0.05$). The mean systolic pressure (141.7 ± 8.3 mmHg), diastolic blood pressure (87.5 ± 4.5 mmHg) and mean fasting blood glucose concentration (7.2 ± 0.8 mmol L^{-1}) in the atypical treatment group were significantly higher than in the conventional treatment group. Likewise, the lipid profile components of total cholesterol (TC) (5.9 ± 0.3 mmol L^{-1}), triglycerides (TG) (2.1 ± 0.3 mmol L^{-1}), HDL-C (1.5 ± 0.1 mmol L^{-1}) and very low density lipoprotein (0.4 ± 0.1 mmol L^{-1}) were significantly higher in the atypical treatment group compared to the conventional treatment group. On the contrary, the mean uric acid concentration in the conventional group (257.0 ± 8.2 μmol L^{-1}) was significantly higher than the mean concentration in the atypical group.

4.7 TREATMENT STRATIFIED PREVALENCE OF COMPONENTS OF METABOLIC SYNDROME

From Figure 4.2, when classified by the NCEP ATP III criteria, the prevalence of metabolic syndrome in the atypical treatment group was 44.4% compared to 18.7% in the conventional treatment group but the difference was not statistically significant ($p = 0.0703$). Likewise when classified by the WHO criteria, no significant differences in the prevalence of metabolic syndrome was observed in the conventional and atypical treatment groups (0.3198). The IDF criteria showed the same trend with a metabolic syndrome prevalence of 55.6% and 27.5% in the atypical and conventional treatment groups respectively but the difference was not statistically significant. Raised TG level was the only component out of the five risk components which showed statistical significance in all the three classification criteria with a prevalence of 66.7% in the atypical treatment group and 24.2% in the conventional treatment group (Table 4.8).

Table 4.7 General characteristics of the study population stratified by type of treatment

Variables	Conventional (n = 91)	Atypical (n = 9)	P value
Age (yrs)	37.5 ± 1.4	41.7 ± 5.4	0.3817
WT (kg)	65.9 ± 1.5	67.7 ± 3.3	0.7181
WC (cm)	85.7 ± 1.3	86.1 ± 4.0	0.9211
HC (cm)	100.0 ± 1.5	104.0 ± 2.6	0.4131
WHR	1.4 ± 0.5	0.8 ± 0.0	0.7451
BMI (kg m^{-2})	24.8 ± 0.6	24.0 ± 1.2	0.6743
SBP (mmHg)	124.6 ± 2.1	141.7 ± 8.3	0.0420
DBP (mmHg)	79.1 ± 0.9	87.5 ± 4.5	0.0199
FBS (mmol L^{-1})	5.4 ± 0.3	7.2 ± 0.8	0.0541
UA (µmol L^{-1})	257.0 ± 8.2	195.8 ± 15.7	0.0441
TC(mmol L^{-1})	4.6 ± 0.1	5.9 ± 0.3	0.0018
TG(mmol L^{-1})	1.3 ± 0.1	2.1 ± 0.3	0.0011
HDL-C (mmol L^{-1})	1.2 ± 0.0	1.5 ± 0.1	0.0028
LDL-C (mmol L^{-1})	2.8 ± 0.1	3.4 ± 0.2	0.0711
VLDL(mmol L^{-1})	0.3 ± 0.0	0.4 ± 0.1	0.0024
MDA(µmol L^{-1})	0.8 ± 0.0	0.9 ± 0.0	0.5929

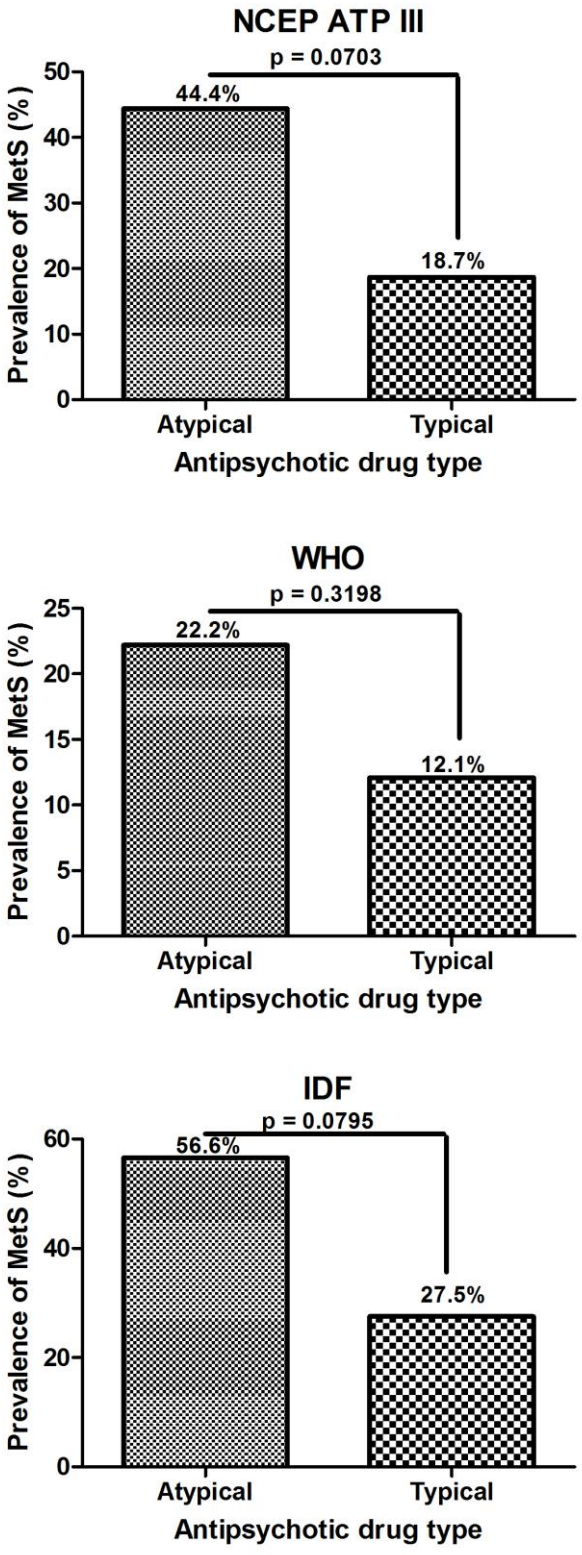

Figure 4.2 Prevalence of metabolic syndrome stratified atypical and typical antipsychotic medication

Table 4.8 Univariate analysis of MetS, its component and Met S score stratified by type of treatment

Variables	Atypical (n = 9)	Typical(n = 91)	OR(95% CI)	P value
National Cholesterol Education Programme Adult Treatment Panel III criteria				
Abdominal obesity	4(44.4%)	27(29.7%)	1.9(0.5-7.6)	0.3606
Raised TG	6(66.7%)	22(24.2%)	6.3(1.4-27.2)	0.0068
Reduce HDL-C	0(0.0%)	17(18.7%)	0.0(0.0-2.0)	0.3507
Raised BP	4(44.4%)	19(20.9%)	3.0(0.7-12.4)	0.1090
Raised FBS	5(55.6%)	24(26.4%)	3.5(0.9-14.2)	0.0657
MetS Score				
0	0(0.0%)	19(20.9%)	0.0(0.0-1.7)	0.2008
1	3(33.3%)	31(34.1%)	1.0(0.1-4.1)	0.9647
2	2(22.2%)	24(26.4%)	0.8(0.1-4.6)	0.7865
≥3	4(44.4%)	17(18.7%)	3.5(0.6-17.9)	0.0703
World Health Organization criteria				
Abdominal obesity	0(0.0%)	18(19.8%)	0.0(0.0-1.8)	0.3570
Raised TG	6(66.7%)	22(24.2%)	6.3(1.4-27.2)	0.0068
Reduce HDL-C	0(0.0%)	17(18.7%)	0.0(0.0-2.0)	0.3507
Raised BP	3(33.3%)	14(15.4%)	2.8(0.4-14.7)	0.1715
Raised FBS	5(55.6%)	24(26.4%)	3.5(0.9-14.2)	0.0657
MetS Score				
0	2(22.2%)	40(44.0%)	0.4(0.0-2.1)	0.2076
1	2(22.2%)	22(24.2%)	0.9(0.1-5.2)	0.8958
2	3(33.3%)	16(17.6%)	2.3(0.3-12.3)	0.2505
≥3	2(22.2%)	13(14.3%)	1.7(0.2-10.4)	0.5247
International Diabetic Federation criteria				
Abdominal obesity	4(44.4%)	42(46.2%)	0.9(0.2-4.7)	0.9218
Raised TG	6(66.7%)	22(24.2%)	6.3(1.4-27.2)	0.0068
Reduce HDL-C	2(22.2%)	47(51.6%)	0.3(0.0-1.5)	0.0921
Raised BP	4(44.4%)	19(20.9%)	3.0(0.7-12.4)	0.1090
Raised FBS	5(55.6%)	26(28.6%)	3.1(0.6-16.8)	0.0950
MetS Score				
0	1(11.1%)	21(23.1%)	0.4(0.0-3.4)	0.4084
1	3(33.3%)	29(31.9%)	1.1(0.2-5.4)	0.9284
2	1(11.1%)	25(27.5%)	0.3(0.0-2.7)	0.2858
≥3	4(44.4%)	16(17.6%)	3.8(0.7-19.3)	0.0546

4.8 CONVENTIONAL, ATYPICAL DRUGS AND THE PREVALENCE OF METABOLIC SYNDROME

Table 4.9 gives the general overview of the prevalence of metabolic syndrome and its components as assessed with the NCEP ATP III criteria based on specific drugs administered to the patients on treatment. Out of the Sixty three (63) patients who were on a monotherapy regimen of conventional antipsychotics, 33.3% were on chlorpromazine, 20.6% were on trifluoperazine, 23.8% were on haloperidol and 6.3% were on fluphenazine. 11.1% on the antidepressant, amitriptyline and 4.8% were on the mood stabilizer, carbamazepine. The highest prevalence of metabolic syndrome (28.6%) was observed in patients on amitriptyline with raised triglyceride concentration being the most prevalent component (57.1%) of metabolic syndrome associated with amitriptyline usage. None of the patients on carbamazepine had metabolic syndrome (0.0%) but raised blood pressure was the most prevalent component (66.7%) linked with carbamazepine use. All the other monotherapy antipsychotics gave varying prevalence of metabolic syndrome with varying prevalence in the components of metabolic syndrome. Trifluoperazine and haloperidol were associated with raised waist circumference; fluphenazine with raised waist circumference, raised triglyceride, raised blood pressure and raised fasting blood glucose and chlopromazine with raised fasting blood glucose.

The prevalence of metabolic syndrome in patients on a polytherapy regimen of conventional antipsychotics was 25% with raised waist circumference being the most prevalent component of metabolic syndrome (35.7%). The highest prevalence of metabolic syndrome in patients on monotherapy of atypical antipsychotic drugs was observed in patients on risperidone (66.7%) with increased triglycerides and raised fasting blood glucose being the prevalent components of metabolic syndrome.

In Table 4.10, the prevalence of metabolic syndrome and its components was assessed using WHO criteria. The highest prevalence of metabolic syndrome in patients on monotherapy of conventional antipsychotics was seen in patients on fluphenazine (25.0%). With patients on polytherapy of conventional antipsychotics, the prevalence of metabolic syndrome was 10.7% with raised triglyceride concentration being the most prevalent component (28.6%). With patients on monotherapy of atypical antipsychotics, risperidone gave the highest prevalence of metabolic syndrome (33.3%) with raised triglyceride and raised fasting blood glucose levels being the most prevalent components of metabolic syndrome.

In using the IDF criteria, trifluoperazine gave the highest prevalence of metabolic syndrome (53.8%) among the monotherapy conventional antipsychotics with increased waist circumference being the most prevalent component of metabolic syndrome (69.2%). None of the patients on carbamazepine had metabolic syndrome and increased waist circumference and raised blood pressure were the most prevalent components of metabolic syndrome linked with the use of carbamazepine. Twenty five (25%) of the patients on polytherapy of conventional antipsychotics had metabolic syndrome with increased waist circumference being the most prevalent component of metabolic syndrome. Risperidone still turned out to be the atypical antipsychotic with the highest prevalence of metabolic syndrome (66.7%) with increased triglyceride concentration being the most prevalent component of metabolic syndrome associated with risperidone usage (Table 4.11).

Table 4.9 Prevalence of metabolic syndrome and components of metabolic syndrome defined by the NCEP ATP III criteria in the study population stratified by drugs

National Cholesterol Education Programme Adult Treatment Panel III Criteria							
Variables	**n**	**MetS(%)**	**↑WC (%)**	**↑TG (%)**	**↓ HDL-C (%)**	**↑ BP (%)**	**↑ FBS (%)**
Typical AP (Monotherapy)							
TRIFLUOPERAZINE	13	2(15.4)	6 (46.2)	2 (15.4)	4 (30.8)	2 (15.4)	4 (30.8)
HALOPERIDOL	15	3(20.0)	6 (40.0)	5 (33.0)	2 (13.0)	2 (13.0)	5 (33.0)
FLUPHENAZINE	4	1(25.0)	1 (25.0)	1 (25.0)	0 (0.0)	1 (25.0)	1 (25.0)
CHLORPROMAZINE	21	2(9.5)	3 (14.3)	2 (9.5)	4 (19.0)	4 (19.0)	5 (23.8)
CARBAMAZEPINE	3	0(0.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)
AMITRIPTYLINE	7	2(28.6)	1 (14.3)	4 (57.1)	2 (28.6)	1 (14.3)	3 (42.9)
Typical AP (Polytherapy)	28	7(25.0)	10 (35.7)	8 (28.6)	5 (17.9)	7 (25.0)	6 (21.4)
Atypical AP (Monotherapy)							
OLANZAPINE	6	2(33.3)	2 (33.3)	3 (50.0)	0 (0.0)	3 (50.0)	3 (50.0)
RISPERIDONE	3	2(66.7)	2 (66.7)	3 (100.0)	0 (0.0)	1 (33.3)	3 (100.0)

AP = anti-psychotic, MetS = Metabolic syndrome, WC = waist circumference, TG = triglycerides, HDL-C = high density lipoprotein cholesterol, BP = blood pressure, FBS = fasting blood glucose

Table 4.10 Prevalence of metabolic syndrome and components of metabolic syndrome defined by the WHO criteria in the study population stratified by drugs

		World Health Organization Criteria					
Variables	**n**	**MetS(%)**	**↑WC (%)**	**↑TG (%)**	**↓ HDL-C (%)**	**↑ BP (%)**	**↑ FBS (%)**
Typical AP (Monotherapy)							
TRIFLUOPERAZINE	13	2(15.4)	7 (53.8)	2 (15.4)	4 (30.8)	2 (15.4)	4 (30.8)
HALOPERIDOL	15	3(20.0)	7(47.0)	5 (33.0)	2 (13.0)	2 (13.0)	5 (33.0)
FLUPHENAZINE	4	1(25.0)	1 (25.0)	1 (25.0)	0 (0.0)	1 (25.0)	1 (25.0)
CHLORPROMAZINE	21	2(9.5)	7 (33.3)	2 (9.5)	4 (19.0)	3 (14.3)	5 (23.8)
CARBAMAZEPINE	3	0(0.0)	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
AMITRIPTYLINE	7	1(14.3)	1 (14.3)	4 (57.1)	2 (28.6)	0 (0.0)	3 (42.9)
Typical AP (Polytherapy)	28	3(10.7)	7 (25.0)	8 (28.6)	5 (17.9)	5 (17.9)	6 (21.4)
Atypical AP (Monotherapy)							
OLANZAPINE	6	1(16.7)	0 (0.0)	3 (50.0)	0 (0.0)	2 (33.3)	3 (50.0)
RISPERIDONE	3	1(33.3)	1 (33.3)	3 (100.0)	0 (0.0)	1 (33.3)	3 (100.0)

AP = anti-psychotic, MetS = Metabolic syndrome, WC = waist circumference, TG = triglycerides, HDL-C = high density lipoprotein cholesterol, BP = blood pressure, FBS = fasting blood glucose

Table 4.11 Prevalence of metabolic syndrome and components of metabolic syndrome defined by the IDF criteria in the study population stratified by drugs

International Diabetic Federation Criteria							
Variables	**n**	**MetS(%)**	**↑WC (%)**	**↑TG (%)**	**↓ HDL-C (%)**	**↑ BP (%)**	**↑ FBS (%)**
Typical AP (Monotherapy)							
TRIFLUOPERAZINE	13	7(53.8)	9(69.2)	2(15.4)	7(53.8)	2(15.4)	5(38.5)
HALOPERIDOL	15	5(33.0)	7(47.0)	6(40.0)	8(53.0)	2(13.0)	5(33.0)
FLUPHENAZINE	4	1(25.0)	2(50.0)	1(25.0)	1(25.0)	1(25.0)	1(25.0)
CHLORPROMAZINE	21	4(19.0)	7(33.3)	2(9.5)	13(61.9)	4(19.0)	5(23.8)
CARBAMAZEPINE	3	0(0.0)	2(66.7)	0(0.0)	1(33.3)	2(66.7)	0(0.0)
AMITRIPTYLINE	7	1(14.3)	2(28.6)	4(57.1)	4(57.1)	1(14.3)	3(42.9)
Typical AP (Polytherapy)	28	7(25.0)	13(46.4)	8(28.6)	12(42.9)	7(25.0)	7(25.0)
Atypical AP (Monotherapy)							
OLANZAPINE	6	2(33.3)	3(50.0)	3(50.0)	2(33.3)	3(50.0)	3(50.0)
RISPERIDONE	3	2(66.7)	2(66.7)	3(100.0)	0(0.0)	1(33.3)	2(66.7)

AP = anti-psychotic, MetS = Metabolic syndrome, WC = waist circumference, TG = triglycerides, HDL-C = high density lipoprotein cholesterol, BP = blood pressure, FBS = fasting blood glucose

Chapter 5

DISCUSSION

5.1 PREVALENCE OF METABOLIC SYNDROME AND ASSOCIATED DISORDERS

The overall prevalence of metabolic syndrome in Ghanaian psychiatric patients on medication as determined with the NCEP ATP III, WHO and IDF criteria were 11.5%, 13.5% and 15.5% respectively. These overall prevalence rates were higher compared to the general Ghanaian population prevalence rates of 3.9%, 2.2% and 7.8% determined with the NCEP ATP III, WHO and IDF criteria respectively **(Owiredu et al., 2009); under review**. When stratified by treatment however, the prevalence of metabolic syndrome determined with the NCEP ATP III (21.0%) and IDF (29.0%) criteria in patients on treatment was significantly higher than the prevalence rate of 2.0% recorded with the NCEP ATP III and IDF criteria in the newly diagnosed patients. Recent population-based research estimated that the prevalence of metabolic syndrome ranges from 29% to 34% among Australians ages over 25 years (Zimmet *et al.*, 2005).

The prevalence of the metabolic syndrome in patients on treatment determined with the NCEP ATP III and IDF criteria in this study compares well with prevalence rates in the general population as stated above and therefore shows them to be a high risk group for cardiovascular disease. Heiskanen et al., (2003) reported the diagnosis of metabolic syndrome in 13 (37%) out of 35 patients with schizophrenia treated with antipsychotic medication and Mackin et al., (2007) reported increased prevalence of metabolic syndrome and cardiovascular risk in 90 people treated with antipsychotics, compared to age and gender matched controls. Correl *et al.* (2006) also reported that metabolic syndrome was present in 137

(37.3%) out of 367 adults treated with second generation antipsychotics and was significantly associated with the 10-year risk of Coronary Heart disease (CHD) events. The prevalence of metabolic syndrome determined by the WHO criteria in patients on treatment (13.0%) and newly diagnosed patients (14.0%) was lower compared to prevalence rates in the general population and almost equal in both populations but the difference was not statistically significant.

The relationship between age and the metabolic syndrome has long been documented by Ford *et al.,* (2002) in their study in the United States finding the prevalence of metabolic syndrome increasing with age and being almost equal in men and women. Alexander *et al.* (2003) in studying the relationship between metabolic syndrome, hyperglycaemia and age, found a metabolic syndrome prevalence of 43.5% (NCEP ATP III criteria) in people older than 50 years of age. Patients on treatment in this study were significantly older than their antipsychotic naïve counterparts and a correlation analysis between age and metabolic syndrome per the three study criteria gave significant positive linear relationships showing the direct relationship between increasing age and the risk of metabolic syndrome.

A further classification of patients on treatment into drug type (conventional and atypical), showed patients on atypical antipsychotics having a higher prevalence of metabolic syndrome compared to those on conventional antipsychotics. The prevalence of metabolic syndrome determined with the NCEP ATP III and IDF criteria in patients on atypical antipsychotics was 44.4% and 55.6% respectively while the WHO criteria gave a prevalence of 22.2%. Apart from the WHO criteria which gave prevalence rates within the range of what has been calculated in the

general population, the NCEP ATP III and IDF criteria gave prevalence rates almost twice what has been calculated in the general population showing them to be a high risk group for metabolic syndrome and its effects.

5.2 PSYCHIATRIC PATIENTS AND MEDICAL CO-MORBIDITY

There is growing evidence that severe mental illnesses are associated with significant physical co-morbidities (Davidson *et al.*, 2001; Mitchell and Malone, 2006) that lead to increased risk of premature mortality in many psychiatric patients (Dembling *et al.*, 1999; Saha *et al.*, 2007). Phelan *et al.* (2001) reported that risk factors for cardiovascular disorders and rates of physical disorders are increased in psychiatric populations, partly due to low levels of help seeking, and lifestyle factors such as poor diet, reduced physical activity and smoking. Weight gain is an established side effect of most of the antipsychotic drugs (including conventional and atypical antipsychotics). This association is well documented for the first generation or conventional antipsychotics and more recently same association has been described for the newer or second generation atypical antipsychotic drugs (Klett and Caffey, 1960; Taylor and McAskill, 2000). In a study of the risk of coronary heart disease (CHD) and stroke in addition to lifestyle factors in 102 patients with schizophrenia, McCreadie (2003) found 70% of the male patients and 86% of the female patients being either overweight or obese. Mackin *et al,* (2007) reported increased prevalence of metabolic syndrome and cardiovascular risk in 90 people treated with antipsychotics, compared to 92 age and gender matched controls. Body mass index (BMI), disorders of lipid and glucose metabolism and risk for cardiovascular disorders were increased in individuals with severe mental illness across the diagnostic spectrum who were treated with antipsychotics as compared to the controls. A Finish study reported

that individuals treated with antipsychotic medications were three times more likely to have high cholesterol or high triglyceride than those who were not taking the drugs (Saari *et al.*, 2004). The reason for the low concentration of MDA observed in patients on treatment compared to their newly diagnosed counterparts in this study is not readily known. However, it could be in part to the effect of the treatment regimen. This assertion should however be further investigated in related studies as it was not critically examined in this study.

Of the co-morbidities assessed in this study, patients on treatment were 12 times at risk of indulging in alcohol, 2.5 times at risk of being obese, 3 times at risk of developing hypercholesterolaemia, low HDL-cholesterol, high LDL-cholesterol and 26 times at risk of developing hyperuricaemia compared to their antipsychotic naïve counterparts. The significant finding of obesity and disorders in lipid profile could be linked with the high prevalence of metabolic syndrome in psychiatric patients on treatment in this study and reveals the increased risk of cardiovascular disorders and premature mortality in psychiatric patients on treatment. Therefore this finding agrees with previous studies (Cohn *et al.*, 2004; Bobes *et al.*, 2007; Newcomer, 2007).

Furthermore, the significant presence of alcoholism and hyperuricaemia could exacerbate metabolic syndrome and its associated risk factors. A close relationship between alcoholism and mental health has been found with people with mental health problems as observed in a U.S study where it was established that around half of individuals with a lifetime addictive disorder also had lifetime mental disorders and vice versa (Kessler *et al.*, 1996). The Epidemiologic Catchment Area report found 19.9% of the general population in the US having one or more

psychiatric disorders, but in those with alcohol abuse or dependence, the figure rose to 36.6% (Regier *et al.*, 1990). A UK study also found the majority of patients presenting with first episode psychosis reported substance use with 43% meeting the criteria for alcohol abuse/dependence at some point in their life (Barnett *et al.*, 2007).

Uric acid has been found to be significantly associated with metabolic syndrome risk factors in industrialized (Matsubara *et al.*, 2002; Yoo *et al.*, 2005) and developing (Conen *et al.*, 2004) countries and is an independent predictor of hypertension in Western civilizations (Sundstrom *et al.*, 2005). Reimann *et al.* (2008) in their study in sub-Saharan Africans concluded that hyperuricaemia was an additional component of metabolic syndrome and should be given more attention.

5.3 DIABETES MELLITUS AND MENTAL ILLNESS

Glucose dysregulation has been demonstrated in antipsychotic naïve schizophrenia patients. Ryan *et al.* (2003) in a study on the prevalence of impaired fasting glucose in drug naïve patients with schizophrenia compared to age-matched healthy controls, found more than 57.7% of the patients with impaired fasting glucose and insulin resistance in addition to higher fasting plasma glucose, insulin and cortisol. Bushe & Holt (2004) also reported that people with schizophrenia and other severe mental disorders are at greater risk of developing diabetes or having impaired glucose tolerance. Contrary to these findings, results from this study showed an equal likelihood in the risk of developing diabetes in antipsychotic naïve patients and those on treatment when diabetes was assessed as co-morbidity for metabolic syndrome. The mean fasting blood glucose in patients on treatment and newly diagnosed patients showed no statistical significance and the prevalence of diabetes as a component of metabolic syndrome defined by the

NCEP ATP III, IDF and WHO criteria showed no statistically significant difference in both study populations. Upon adjusting for age in a logistic regression analysis, raised fasting blood glucose did not turn up as a significant risk factor for metabolic syndrome. This major finding could therefore explain the inability of the WHO criteria to clearly define metabolic syndrome in patients on treatment and newly diagnosed patients since it states that individuals should be diabetic. In addition to equal risk of diabetes development being detected, there was also an almost equal rate of metabolic syndrome prevalence.

5.4 ATYPICAL ANTIPSYCHOTICS AND DIABETES MELLITUS

Case reports have emerged which points to elevated levels of hyperglycaemia and diabetes mellitus associated with the use of atypical antipsychotics. Lindenmayer & Patel (1999) reported a case of olanzapine-induced diabetic ketoacidosis (DKA), which resolved following discontinuation of olanzapine treatment and further discussed the role of olanzapine in suppressing insulin release and in producing a hyperglycaemic response. The mean fasting blood glucose level in patients on atypical antipsychotics in this study was significantly higher compared to those on typical antipsychotics. A high prevalence of increased fasting blood glucose was associated with Risperidone use compared to olanzapine use in this study. Contrarily, Koro *et al.,* (2002b) in a large population based nested case-control study found olanzapine to be associated with a significant risk of diabetes compared with Risperidone.

5.5 ANTIPSYCHOTICS AND WEIGHT GAIN

Weight gain, especially visceral adiposity as measured by waist circumference is one of the key components of metabolic syndrome and is the main criterion in the

IDF definition. Comments on change in weight in psychiatric patients during the course of a psychotic illness (Kraepelin, 1919) have evoked significant interest in weight gain associated with the use of atypical antipsychotic drugs. Zhang *et al., (2004)* studied drug naïve Chinese psychiatric in-patients before and following 10 weeks of antipsychotic treatment by comparing them to well matched healthy controls. After 10 weeks of treatment the patient group showed significant increases in abdominal subcutaneous fat and intra-abdominal fat, plasma leptin levels, plasma glucose levels and plasma lipid levels. Interestingly, no significant difference was found between Risperidone and Chlorpromazine and no significant correlation was observed between change in BMI and clinical improvement. Likewise in this study, there were no significant differences in weight, waist circumference and BMI when compared in patients on atypical and conventional antipsychotics. Upon adjusting for age in a logistic regression, however, waist circumference defined by the NCEP ATP III, IDF and WHO criteria and BMI were significant predictors of metabolic syndrome showing the ability of atypical and conventional antipsychotics to have an almost equal propensity in inducing weight gain in patients on medication.

5.6 ANTIPSYCHOTICS AND TRIGLYCERIDES

Dyslipidaemia is an important component of the metabolic syndrome and occurs along with glucose dysregulation and weight gain in patients treated with atypical antipsychotics. In the North Finland 1966 Birth Cohort, subjects treated with antipsychotics, both conventional and atypical were found to have increased lipid levels. A total of 8463 subjects from the original cohort participated in this study. Out of 5654 (67%) of the total number of participants, 45 subjects were receiving antipsychotic treatment. 32 subjects (71%) were on conventional, 6 subjects (13%)

were on atypical and 7 subjects (16%) were on both conventional and atypical antipsychotic treatment. The study found high prevalence of total cholesterol and triglycerides in the 45 subjects treated with antipsychotics as compared to the 5609 who were not, even after adjusting for risk factors for hyperlipidaemia. Contrary to this finding, this study found significantly elevated total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol and VLDL in patients on atypical antipsychotics compared to those on conventional antipsychotics. A logistic regression analysis with adjustment for age also showed hypertriglyceridaemia and reduced HDL-cholesterol being significant risk factors for metabolic syndrome. Following case reports of elevated lipids associated with antipsychotic treatment, Koro *et al., (2002a)* explored the association using the General Practice Research Database (GPRD) and found patients treated with atypical antipsychotics being almost 3 times at risk of developing hyperlipidaemia compared to patients treated with conventional antipsychotics which is in line with the findings in this study. Tarricone et al. (2006) compared the prevalence of hyperglycaemia, hypercholesterolaemia and hypertriglyceridaemia and found that patients treated with atypical antipsychotics had a significant prevalence of hyperglycaemia and hypertriglyceridaemia compared to controls. Saari *et al., (2004)* in their study suggested that increased lipids impair glucose metabolism leading to hyperglycaemia and type 2 diabetes mellitus. This finding could therefore explain the significant finding of diabetes observed in patients on atypical antipsychotics compared to those on conventional antipsychotics.

5.7 ANTIPSYCHOTICS AND HYPERTENSION

Hypertension is one component of metabolic syndrome which has not been commonly associated with treatment with atypical antipsychotics in general

literature. In a retrospective chart review of 208 patients suffering from schizophrenia and treated with antipsychotics (conventional and atypical), Gupta *et al., (2003)* found increased prevalence of diabetes (17%), hypertension (29%) and hypertriglyceridaemia (44%). The study however, did not find significant differences between the two antipsychotic generations. Contrary to those findings, patients on atypical antipsychotics in this study had significantly elevated systolic and diastolic blood pressure when compared to those on conventional antipsychotics. When blood pressure was analyzed as a risk component of metabolic syndrome, the prevalence of raised blood pressure as determined by the NCEP ATP III, WHO and IDF criteria was 2 times higher in patients on atypical antipsychotics compared to those on conventional antipsychotics.

Chapter 6

CONCLUSION AND RECOMMENDATION

6.1 CONCLUSION

Risk factors for metabolic syndrome development in this study were hypertriglyceridemia, low HDL-cholesterol and raised blood pressure.

Antipsychotic medication that led to metabolic syndrome development in this study according to the ATP III, WHO and the IDF definition criteria for metabolic syndrome were Amitryptyline (28.6%), Fluphenazine (33.3%) and Trifluoperazine (53.8%) respectively.

The use of antipsychotics, especially atypical antipsychotics should be re-examined with the knowledge that they can cause significant metabolic abnormalities and metabolic syndrome in patients. Different atypical antipsychotics differ in their propensity to be associated with or even cause weight gain, diabetes mellitus and dysplipidaemia and considering the limited number of psychiatric patients on atypical antipsychotics in this study, there is the need for further studies on metabolic abnormalities of atypical antipsychotics in a larger cohort of psychiatric patients in the country.

Alcoholism and hyperuricaemia should also be given prioritized attention in Ghanaian psychiatric patients. Furthermore, the WHO criteria, based on its definition does not properly define metabolic syndrome among Ghanaian psychiatric patients as observed in this study and must further be researched into in psychiatric patients to properly reflect the prevalence of metabolic syndrome.

Management should also include the ability for recognition, prevention and the treatment of the individual components of the metabolic syndrome according to established practice as well as promote the usage of antipsychotics least likely to cause these problems.

6.2 MANAGEMENT OF METABOLIC SYNDROME

Various guidelines, consensus statements and recommendations have been published on the management of metabolic syndrome and consist of:

1. Baseline monitoring and regular follow up (history, physical examination, blood tests)
2. Primary management (lifestyle interventions – weight loss, increased physical activity, smoking cessation and modification of diet)
3. Secondary management (treatment of individual components of metabolic syndrome – diabetes, obesity, dyslipidaemia and hypertension).

The Consensus Statement on antipsychotic drugs, obesity and diabetes (2004) reiterated the importance of antipsychotic medication in psychiatric treatment and acknowledges the increased risk of obesity, diabetes and dyslipidaemia following treatment with atypical antipsychotics and recommends baseline screening and follow-up on treatment.

The risk of atherosclerotic cardiovascular disease (ASCVD) is increased 2 fold and the risk of diabetes increased 5 fold by the presence of metabolic syndrome (Grundy *et al.*, 2005). The Scientific Statement by the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) advises reduction in ASCVD risk factors and lifestyle interventions as the important goals in the management of metabolic syndrome. The suggestions include smoking cessation and restoration of lipid levels, blood glucose and hypertension to the healthy range. The lifestyle interventions include weight loss, increased physical activity and modification of diet.

6.3 RECOMMENDATION FOR FURTHER STUDIES

It is recommended that further studies would be done in the relationship between metabolic syndrome, mental illness and their association with adiponectin, resistin and leptin in a larger cohort of psychiatric patients in the country.

Thyroid hormone levels and their association with mental illness and thus metabolic syndrome should also be studied further amongst the psychiatric population in the country.

It is also recommended that urine chromatography be done on psychiatric patients to identify those with metabolic syndrome.

The recommendations of the IDF (Alberti *et al.*, 2006) are similar to that in the AHA/NHLBI consensus statement. Healthy lifestyle promotion is recommended as the primary management for metabolic syndrome by the IDF, comprising of calorie restriction, increased physical activity and dietary modification. Treatment of individual components of metabolic syndrome using medication is advised for people not responding to lifestyle interventions. The IDF stresses on the need for further studies from around the world to help improve the management of metabolic syndrome.

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